COUGH REFLEX TESTING IN ACUTE DYSPHAGIA MANAGEMENT: VALIDITY, RELIABILITY AND CLINICAL APPLICATION

A thesis submitted in partial fulfilment of the requirements for the Degree of Doctor of Philosophy in Speech and Language Pathology at the University of Canterbury

by

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2013

PREFACE

This PhD thesis conforms to the referencing style recommended by the American Psychological Association Publication Manual (6th ed.) and spelling recommended by the Oxford English Dictionary.

The research was carried out between January 2010 and December 2012 at four New Zealand hospitals: Middlemore Hospital, North Shore Hospital, Auckland City Hospital, Christchurch Hospital and at a number of international professional development events (New Zealand, Australia, England, Ireland and United States of America). The research was supervised by Dr. Maggie-Lee Huckabee, Senior Lecturer & Researcher, The University of Canterbury and Dr. Jacqui Allen, Honorary Lecturer & Researcher, Department of Surgery, The University of Auckland. Financial support was provided by a New Zealand District Health Board (DHB) Research Fund Translational Research Grant (DHBNZ 09-658), a Waitemata DHB Allied Health Development Fund, a New Zealand Speech-language Therapists' Association research grant and a Maurice and Phyllis Paykel Trust travel grant-in-aid.

Preliminary results from this PhD research have been presented at the following national and international conferences:

Miles, A., McLauchlan, H. & Huckabee, M-L. (2010) Identifying aspiration and reducing pneumonia in stroke patients using cough reflex testing. Platform presentation. 4th Biomouth Symposium, Christchurch, New Zealand, 8th-9th June 2010

Miles, A., McLauchlan, H. & Huckabee, M-L. (2011) Identifying aspiration and reducing pneumonia in stroke patients using cough reflex testing: preliminary results. Platform presentation. 8th Asia Pacific Speech, Language and Hearing Conference, Christchurch, New Zealand, 11th-14th January 2011

Miles, A., McLauchlan, H. & Huckabee, M-L. (2011) Reducing pneumonia by changing clinical practice: Introducing a new tool. Platform Presentation. Stroke Society of Australasia 2011 Annual Scientific Meeting, Adelaide, Australia, 14th-16th September 2011

Miles, A., McLauchlan, H. & Huckabee, M-L. (2012) Identifying aspiration and reducing pneumonia in stroke patients using cough reflex testing. Poster presentation. 20th Dysphagia Research Society annual meeting, Toronto, Canada 7th-12th March 2012

Miles, A., Moore, S., McLauchlan, H. & Huckabee, M-L. (2012) Identifying aspiration and reducing pneumonia using cough reflex testing: integrating a new tool into clinical practice. Workshop. New Zealand Speech-language Therapist' Association Beyond Boundaries Conference, Auckland, New Zealand, 23rd-25th May 2012

Miles, A., Moore, S., McFarlane, M., Lee, F. & Huckabee, M-L. (2012) A bedside tool for identifying silent aspiration; Validating cough reflex testing against instrumental assessment of aspiration and laryngeal sensation. Platform presentation. 6th Biomouth Symposium, Auckland, New Zealand, 28th-29th November 2012

Miles, A., Moore, S., McFarlane, M., Lee, F. & Huckabee, M-L. (2013) A bedside tool for identifying silent aspiration; Validating cough reflex testing against instrumental assessment

of aspiration and laryngeal sensation. Platform presentation. 21st Dysphagia Research Society annual meeting, Seattle, USA, 13th-16th March 2013

Original articles:

Miles, A. & Huckabee, M-L. (2013) Intra- and inter-rater reliability for judgement of cough following citric acid inhalation. International Journal of Speech-Language Pathology, 15 (2); 209-215. DOI: http://dx.doi.org/10.3109/17549507.2012.692812

Miles, A., Zeng, I.S.L, McLauchlan, H. & Huckabee, M-L. (2013) Cough reflex testing in dysphagia following stroke: A randomized controlled trial. Journal of Clinical Medicine Research, 5 (3); 222-233. DOI: http://dx.doi.org/10.4021/jocmr1340w

Miles, A., Moore, S., McFarlane, M., Lee, F., Allen, J. & Huckabee. M-L. (early online) Validating cough reflex testing against instrumental assessment of aspiration. Physiology and Behaviour. DOI: http://dx.doi.org/10.1016/j.physbeh.2013.05.004

The following publications are under review:

Miles, A., McLauchlan, H. & Huckabee, M-L. (under revision) Clinical outcomes for patients with dysphagia after stroke in New Zealand: original article. Speech Language & Hearing. Revision submitted on 12th August 2013.

Miles, A., McFarlane, M. & Huckabee, M-L. (under review) Intra- and inter-rater reliability for judgement of cough following citric acid inhalation following training. Dysphagia. Submitted 2nd August 2013.

Abstracts:

Miles, A., McLauchlan, H. & Huckabee, M-L. (2010) Identifying aspiration and reducing pneumonia in stroke patients using cough reflex testing. Conference Proceedings. New Zealand Dental Journal, Dec, p.147

Miles, A., McLauchlan, H. & Huckabee, M-L. (2011) Identifying aspiration and reducing pneumonia in stroke patients using cough reflex testing (abstract). International Journal of Stroke, 6 (Suppl 1), 21-22

Miles, A., McLauchlan, H. & Huckabee, M-L. (2012) Identifying aspiration and reducing pneumonia in stroke patients using cough reflex testing. Dysphagia, 27, p. 606

ABSTRACT

Silent aspiration is associated with pneumonia and mortality, and is poorly identified by traditional clinical swallowing evaluation (CSE). Currently, there is no reliable test for detecting silent aspiration during CSE. There is, however, increasing evidence for the validity of cough reflex testing (CRT) for identifying silent aspiration. This test has the potential to significantly improve clinical assessment of dysphagia. The aim of this research programme was to further investigate the validity, reliability and clinical utility of CRT for identifying patients at risk of silently aspirating.

Several aspects of CRT were explored during this research programme. Two correlational studies were conducted to validate CRT for identifying silent aspiration against videofluoroscopic swallowing study (VFSS) and flexible endoscopic evaluation of swallowing (FEES). Cough reflex threshold testing was completed on 181 patients using inhaled, nebulised citric acid. Within one hour, 80 patients underwent VFSS and 101 patients underwent FEES. All tests were recorded and analysed by two researchers blind to the result of the alternate test. Significant associations between CRT result and cough response to aspiration on VFSS ($p = .003$) and FEES ($p < .001$) were identified. Sensitivity and specificity were optimised at 0.6mol/L in patients undergoing VFSS (71%, 60% respectively) and at 0.4mol/L in patients undergoing FEES (69%, 71% respectively). A concentration of 0.8mol/L had the highest odds ratio (OR) for detecting silent aspiration (8 based on VFSS, 7 based on FEES). Coughing on lower concentrations of citric acid (0.4mol/L compared with 1.2mol/L) was a better predictive measure of silent aspiration.

Diminished cough strength has also been associated with aspiration and increased risk of pneumonia. Reflexive cough is our primary defensive mechanism against aspiration and a measure of reflexive cough strength therefore holds greater relevance than one of voluntary cough strength. Despite common use and clinical applicability, the reliability of subjective cough judgements has received little attention. The inter- and intra-rater reliability of subjective judgements of cough in patients following inhalation of citric acid was assessed. Forty-five speech-language therapists (SLTs) were recruited to the first study. Of these, 11 SLTs were currently using CRT in their clinical practice (experienced raters) and 34 SLTs reported no experience with CRT (inexperienced raters). Participants provided a rating of strong, weak or absent to ten video segments of cough responses elicited by inhalation of nebulised citric acid. The same video segments presented in a different sequence were re-evaluated by the same clinicians following a 15-minute break. Inter-rater reliability for experienced raters was calculated with a Fleiss' generalised kappa of .49; intra-rater reliability was higher with a kappa of .70. Inexperienced raters showed similar reliability with kappa values for inter-rater and intra-rater reliability of .36 and .62, respectively. SLTs demonstrated only fair to moderate reliability in subjectively judging a patient's cough response to citric acid. Experience in making cough judgements did not improve reliability significantly.

In a second study, specific training in cough physiology and cough judgement was provided to 58 trained SLTs. Inter-rater reliability of subjective judgements of cough in patients following inhalation of citric acid was assessed. Participants provided a rating of present or absent, and if present then a rating of strong or weak, to ten video segments of cough responses. Inter-rater reliability for cough presence was calculated with a Fleiss' generalised kappa of .71 and cough strength was calculated at .61. Years of clinical experience did not

improve inter-rater reliability significantly. Experience in using CRT did improve inter-rater reliability. Further validity and reliability research would be beneficial for guiding clinical guidelines and training programmes.

By identifying patients at risk of silent aspiration, more informed management decisions can be made that consequently lead to a reduction in preventable secondary complications such as pneumonia. The clinical utility of CRT for reducing pneumonia in acute stroke patients was assessed through a randomised, controlled trial. Three hundred and eleven patients referred for swallowing evaluation were assigned to either 1) a control group receiving standard evaluation or 2) an experimental group receiving standard evaluation with CRT. Participants in the experimental group were administered nebulised citric acid with test results contributing to clinical decisions. Outcomes for both groups were measured by pneumonia rates at three months post stroke and other clinical indices of swallowing management. Analysis of the data identified no significant differences between groups in pneumonia rate ($p = .38$) or mortality ($p = .15$). Results of CRT were shown to influence diet recommendations ($p < .0001$) and referrals for instrumental assessment ($p < .0001$). Despite differences in clinical management between groups, the end goal of reducing pneumonia in post stroke dysphagia was not achieved.

Through this research, the characteristics and outcomes associated with dysphagia secondary to stroke in New Zealand were identified. Baseline characteristics of 311 patients with dysphagia following acute stroke were collected during their hospital stay and outcomes were measured at three months post stroke. Mortality rates were 16% and pneumonia rates 27%. Mean length of stay was 24 days and only 45% of patients were in their own home at three months post stroke. Pneumonia was significantly associated with mortality and

increased length of stay. Only 13% of patients received referral for instrumental assessment of swallowing. These data are discussed in reference to the National Acute Stroke Services Audit 2009 and internationally published data. The outcomes for stroke patients with dysphagia in New Zealand are poor with a high risk of pneumonia and long hospital stays when compared internationally.

In summary, this research programme has contributed to our understanding of the use of CRT in patients with dysphagia. The addition of a measure of reflexive cough strength may add to clinical assessment but specific training is required to reach adequate reliability. CRT results are significantly associated with aspiration response on instrumental assessment and lower concentrations of citric acid provide a better predictive measure of silent aspiration. CRT can be standardised and therefore is not as susceptible to interpretative variance that plagues much of CSE. Sensitivity and specificity values using this CRT methodology are adequate for CRT to be incorporated into clinical protocols. Inclusion of CRT alone was not shown to be sufficient to change clinical outcomes however integration of CRT into clinical pathways may prove more successful. Further research evaluating the addition of CRT to a comprehensive CSE would add greatly to the field of dysphagia assessment.

ACKNOWLEDGEMENTS

It is diffcult to express my gratitude to Dr Maggie-Lee Huckabee. Despite a lot of hard work, it has been a hugely rewarding four years. Maggie-Lee has taught me many things alongside research skills: scientific writing, presenting research, teaching, supervising students, as well as continued my passion for treating patients with dysphagia. She has inspired me to pursue an academic career after many years working clinically. I am indebted to Maggie-Lee for her enthusiasm and dedication to the subject and to the enormous amount of time she has given me. I would also like to thank Dr. Jacqui Allen who has provided great insights into the research findings and has provided me with considerable professional and personal support. I wish to express my sincere gratitude to both my supervisors for their guidance in my career to date and hopefully for many years to come.

I am appreciative to the speech-language therapists who participated in the studies either by recruiting patients or rating videos. Thank you especially to the team leaders and professional supervisors at the four New Zealand District Health Boards (DHBs) for allowing us to complete research at their work places. A specific thanks goes to Helen McLauchlan. In 2009, when Maggie-Lee approached the two of us to participate in a research project, I did not contemplate that it would lead to this thesis. I thank Helen for her part in making this happen and for always believing in the professional decisions that I have made in my career. I am most grateful for the statistical support provided by Irene Zeng, Counties Manukau DHB and Dr Lifeng Zhou, Waitemata DHB. Irene has provided continued support throughout my studies as well as positive encouragement during times in data analysis when it was greatly welcomed.

I wish to thank all the research participants for consenting and participating in the clinical trials. I appreciate their willingness and so often their enthusiasm for the research programme despite the unfortunate circumstances they were in.

I wish to acknowledge the financial support provided by: my employer- the School of Psychology at University of Auckland, the Health Disability Research Council, New Zealand Speech-language Therapist's Association, Waitemata DHB Allied Health department and Maurice and Phyllis Paykel Trust. I would also like to acknowledge the invaluable resources of Waitemata DHB Allied Health department. This research could not have been completed without their FEES equipment and clinical facilities.

I would like to thank Sara Moore. Many times I have been grateful to have someone as positive as Sara researching in the field of cough reflex testing alongside me. It was a rewarding experience combining our data for analysis and publication and I thank Sara for allowing me to report her data in my thesis. My PhD thesis would not have been completed without the expertise and support of Mary McFarlane. Mary supervised my nasoendoscopy competences to allow collection of data for Study II and contributed considerably to the data collection. She engaged in hours of exchanges of thoughts and helped me to develop my ideas through her wisdom, enthusiasm and friendship.

Finally, I thank my family for accepting my decision to study despite its impact on family life. Thank you, Tim, for your acceptance of having the only four and seven old who can distinguish an endoscopy from a videofluoroscopy and can fall asleep to 15-second bursts of recorded nebuliser noise. I could not have completed this venture without you.

CONTENTS

LIST OF TABLES

CHAPTER ELEVEN

CHAPTER THIRTEEN

LIST OF FIGURES

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CHAPTER EIGHT

CHAPTER ELEVEN

CHAPTER THIRTEEN

ABBREVIATIONS

ACE	Angiotensin-converting enzyme	
AUC	area under curve	
C2	2 coughs= pass	
C5	5 coughs= pass	
CN	Cranial Nerves	CN V Trigeminal nerve
		CN VII Facial nerve
		CN IX Hypoglossal nerve
		CN X Vagus nerve
		CN XI Accessory nerve
		CN XII Hypoglossal nerve
		C1 Cervical spinal nerve 1
		C2 Cervical spinal nerve 2
COPD	chronic obstructive pulmonary disease	
CRT	cough reflex testing	
CSE	clinical swallowing evaluation	
DHB	District Health Board	
EMG	electromyography	
ER	expiratory reflex	
ERS	European Respiratory Society	
FEES	fibreoptic endoscopy evaluation of swallowing	
FEESST	fibreoptic endoscopy evaluation of swallowing with sensory testing	
fMRI	functional magnetic resonance imaging	
κ	kappa coefficient	

LAR	laryngeal adductor reflex
LOS	length of stay
NA	nucleus ambiguous
NTS	nucleus tractus solitaries
OR	odds ratio
PAS	penetration-aspiration scale
RAR	rapidly adapting receptors
RLN	recurrent laryngeal nerve
SAR	slowly adapting receptors
SLN	superior laryngeal nerve
SLT	speech-language therapist
UES	upper oesophageal sphincter
VFSS	videofluoroscopic study of swallowing

PART A: INTRODUCTION AND LITERATURE REVIEW

CHAPTER ONE

INTRODUCTION

Dysphagia is associated with pneumonia, mortality and longer hospital stays. Aspiration, particularly silent aspiration, is associated with increased pneumonia and mortality. Unfortunately, traditional clinical swallowing evaluation is not able to effectively identify patients who silently aspirate. There is, however, increasing evidence of the validity of CRT for identifying silent aspiration. Methodological limitations in previous studies prevent CRT from being easily translated into clinical protocols. Researchers have used sub-optimal methods for the neurologically impaired patient and have not justified dosage of tussive agent utilised. This research programme addressed the validity, reliability and clinical utility of CRT for identifying patients at risk of silently aspirating.

Part A provides a literature review beginning with an introduction to swallowing physiology and airway protection as a clinical foundation for this thesis. Dysphagia and its consequences are reviewed with a particular focus on stroke and current literature on dysphagia assessment and its limitations are explained. An overview of cough physiology is provided to support the methodology of the research studies. Dystussia (impaired cough) has a significant impact on airway protection in those with dysphagia. Both impaired cough sensitivity and impaired cough strength are described in relation to dysphagia. Finally, cough testing methodology and existing literature on cough testing in dysphagia are presented. This will build the methodological basis for study designs and protocols in this thesis. Again, testing of both cough sensitivity and cough strength is discussed.

Part B, C and D include five methodological studies looking at three aspects of CRT as part of dysphagia assessment: validity, reliability and clinical utility. This research improved

upon the methodologies used previously in CRT for dysphagia assessment and used a controlled CRT protocol appropriate for a neurological population. In Part B, Studies I and II investigated the validity of CRT against two previously validated instrumental measures of aspiration (videofluoroscopy and videoendoscopy). The diagnostic accuracies of a range of concentrations of citric acid for identifying patients at risk of silent aspiration are reported. Cough strength has been associated with increased aspiration and pneumonia risk and thus a subjective judgement of cough strength was included to the CRT protocol in the experimental studies. In Part C, Study III investigated the inter- and intra-reliability of subjective judgements of cough following citric acid inhalation in SLTs without any specific training. Study IV investigated if the inter-rater reliability of SLTs improved when specific training was provided. In Part D, Study V investigated the clinical utility of CRT for reducing pneumonia in patients with dysphagia after stroke. This randomised control trial compared functional outcomes for patients with and without CRT as a component of acute swallowing assessment. A discussion of the results of the research programme is provided in Part E. Introduction of a new tool comes with the challenge of changing clinical practice. Literature on changing clinical practice and the complexity of clinical decision-making are reviewed while discussing the possible barriers to implementation of CRT by the clinicians in the studies.

Study V uncovered valuable national data regarding clinical outcomes and clinical practices for patients with dysphagia after stroke in New Zealand. As a subordinate project, in Part F, Study VI defined these clinical outcomes and compared them to international standards. These outcomes have not been previously reported.

Finally, the clinical applicability of the results of this research programme and directions for future research are discussed. Adequate swallowing assessment remains a problem in dysphagia management with sub-optimal identification of silent aspiration by CSE, low instrumental assessment rates, and at a national level, high pneumonia rates when compared with published international data. Cough reflex testing with cough strength judgement is a valid and reliable tool for identifying silent aspiration in patients with dysphagia. CRT methodology described in this thesis is appropriate for the neurological patient and can be incorporated into clinical protocols.

CHAPTER TWO

SWALLOWING PHYSIOLOGY

Swallowing is a rapid, complex neuromuscular process involving 34 pairs of muscles, five cranial nerves, two cervical nerves and coordination between the brainstem and swallowing control regions in the cortex (Daniels & Huckabee, 2008; Lowell et al., 2008). In studying the impact of neurological disease on swallowing and cough, a clear understanding of the physiology of swallowing is essential. To conceptualise this complex process, swallowing can be discussed in terms of phases: pre-oral, oral, pharyngeal and oesophageal (Daniels & Huckabee, 2008).

2.1 Pre-Oral Phase

Before the bolus enters the mouth, a number of sensory inputs may already be activated through smell (olfactory nerve CN I) and sight (occipital nerve CN II). The primary visual and olfactory cortices receive these inputs and information is processed in preparation for the arrival of the bolus into the oral cavity (Daniels & Huckabee, 2008). Depending on the information received, motor efferents may initiate salivary production (facial nerve CN VII and glossopharyngeal nerve CN IX) and/or anticipatory airway closure (vagus nerve CN X) (Daniels & Huckabee, 2008).

2.2 Oral Phase

The motor aspects of the oral phase of swallowing are under voluntary control (Perlman & Schilze-Delrieu, 2003). The muscles of the lips (CN VII), cheeks (CN VII), jaw (trigeminal nerve CN V, hypoglossal nerve XII, cervical nerves C1 and C2) and intrinsic and extrinsic tongue (CN XII) hold the bolus within the oral cavity. They control and prepare the bolus for swallowing (Perlman & Schilze-Delrieu, 2003). The bilateral

palatoglossus muscles (CN IX) contract to ensure the tongue base and soft palate maintain contact throughout bolus preparation, preventing the bolus from entering the pharynx prematurely (Daniels & Huckabee, 2008). Contraction of styloglossus muscles (CN XII), stylohyoids and posterior belly of digastrics (CN VII) also support this closed port (Daniels & Huckabee, 2008). Inadequacy of this seal may lead to aspiration of the bolus before airway closure is completed (Daniels & Huckabee, 2008).

Meanwhile, stimulation of taste receptors across the tongue (CN VII, CN IX) and abundant pressure receptors across the tongue and palate (CN V, CN VII, CN IX) synapse either directly or indirectly in the NTS, allowing the motor response to be modulated for each specific bolus (Daniels & Huckabee, 2008; Perlman & Schilze-Delrieu, 2003). Once the bolus is prepared, the tongue base is pulled downwards, the tongue squeezes against the palate in a backwards motion, pushing the bolus into the pharynx (CN XII) (Perlman & Schilze-Delrieu, 2003).

2.3 Pharyngeal Phase

The pharyngeal phase of swallowing is rapid and involves a complex sequence of movements. Pharyngeal swallowing is initiated by a combination of sensory inputs from CN V, CN VII, CN IX during the oral phase of swallowing and can be cortically modulated for bolus type and size (Perlman & Schilze-Delrieu, 2003). It is thought that deep tongue receptors during the downwards motion of the tongue may also play a part in initiating swallowing (Daniels & Huckabee, 2008). Without timely triggering of swallowing, the bolus again risks entering the airway before airway protection has been fully completed (Daniels & Huckabee, 2008).

Superior and anterior hyoid movement (CN V, CN VII, CN XII, C1, C2) often begins early in the pharyngeal swallowing sequence (Leonard & Kendall, 2008). At its

maximum point, this leads to full deflection of the epiglottis and opening of the upper oesophageal sphincter (UES). The palate rises (CN IX, CN X) to close off the nasal passages and allows the bolus to leave the oral cavity (Perlman & Schilze-Delrieu, 2003). Sensory information in the pharynx (CN V, CN IX, CN X) not only leads to elicitation of pharyngeal swallowing but also modulation of airway closure, pharyngeal constriction and clearance swallows (Daniels & Huckabee, 2008).

The transit of the bolus through the pharynx is a closely coordinated sequence of events. The base of tongue pushes against the posterior pharyngeal wall providing the positive pressure and the driving force for the bolus through the pharynx. At the same time the pharyngeal muscles contract to achieve pharyngeal shortening (Ekberg, 2012). This provides a compliant tube for the bolus to travel through and brings the UES towards to base of tongue to meet the bolus (Ekberg, 2012).The superior, middle and inferior constrictors then sequentially constrict to clear the bolus through the pharynx and through the compliant, open UES (Kahrilas, 1993). Inadequacies in any of these motor and sensory functions may lead to reduced airway protection, residue remaining in the pharynx post swallowing and aspiration risk (Daniels & Huckabee, 2008).

2.4 Oesophageal Phase

The final stage of swallowing is the oesophageal phase. This involves an involuntary peristaltic wave of muscle contraction taking the bolus from the UES to the stomach (Logemann, 1998). The oesophagus begins as striated muscle in the cervical oesophagus but transitions to smooth muscle in the thoracic oesophagus (Goyal & Chaudhury, 2008). The oesophagus is innervated predominately by vagal efferents projecting from the nucleus ambiguous (NA) (Goyal & Chaudhury, 2008). Redirection of food, fluids or acidic stomach contents back into the pharynx leads to aspiration risk (Logemann, 1998).

2.5 Neural Control

In studying swallowing after neurological injury, an understanding of neurophysiology is critical. The basic motor plan for swallowing is controlled by a central pattern generator in the medulla of the brainstem (Daniels & Huckabee, 2008). As a result, injury to the brainstem results in impairments of swallowing as well as cough and respiration (Cichero & Murdoch, 2006). Neurones involved in swallowing have been found in the bilateral nuclei of tractus solitarius (NTS) and NA (Perlman & Schilze-Delrieu, 2003). The NTS receive all afferent signals from the pharynx and larynx and is the primary sensory nucleus for CN VII, CN IX and CN X (Daniels & Huckabee, 2008). NTS receive secondary input from trigeminal sensory nuclei in the pons. The NA are the primary motor nuclei for CN IX, CN X and CN XI. The NA has extensive interconnections with the NTS for CN V, CN VII and CN XII. The primary sensory nuclei for the superior laryngeal nerve (SLN) of CN X are in the NTS but these nerves also connect directly to the NA for initiation of reflexive cough (Daniels & Huckabee, 2008).

The role of the cortex in swallowing is not easily understood. Swallowing involves complex motor and sensory processing, motor planning and initiation, motor control and coordination. Timely coordinated swallowing requires efficient feed-forward/ feedback loops between the brainstem and cortex through the cortico-bulbar tract as well as between distinct areas in the cortex (Malandraki, Johnson, & Robbins, 2011). Damage to the cortex may also result in swallowing impairments (Lowell et al., 2008). Using functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), a number of areas of bilateral activation have been consistently found during swallowing: pre-motor cortex, primary motor cortex, primary sensory cortex, operculum, supplementary motor area, cingulate cortex, parietal-occipital regions, insula cortex, thalamus and cerebellum during

volitional swallowing (Hamdy et al., 1999; Kern, Jaradeh, Arndorfer, & Shaker, 2001; Lowell et al., 2008; Malandraki, Sutton, Perlman, Karampinos, & Conway, 2009; Sawcruk & Mosier, 2001).

Imaging studies are especially difficult in swallowing. Limitations in temporal sensitivity make separating components of the rapid swallowing process difficult and add complexity to analysis and interpretation (Huckabee, Deecke, Cannito, Gould, & Mayr, 2003). Subjects are required to lie supine and the effect of this abnormal swallowing position on neural activity is unknown. Subjects are often required to follow visual or auditory cues during procedures and the effect of these cues on parietal-occipital activation is also unknown (Malandraki et al., 2009). Finally, imaging of truly reflexive swallowing events has proven difficult in this controlled environment and most studies report activation during voluntary swallowing tasks only (Kern et al., 2001).

The primary sensorimotor areas were traditionally thought to be activated during the volitionally controlled oral phase of swallowing while pharyngeal, reflexive swallowing relies primarily on brainstem control (Kern et al., 2001). However there is now strong evidence to the contrary. Hamdy and colleagues have contributed greatly to this field of study. They have used transcranial magnetic stimulation (TMS) and electromyography to map the organisation of the primary motor cortex projections for oral, pharyngeal and oesophageal swallowing muscles (Hamdy, Rothwell, Aziz, & Thompson, 2000; Hamdy et al., 1999). Malandraki and colleagues have also contributed to our enhanced understanding of the neural control of different components of the swallowing process (Malandraki et al., 2009). Recently, they compared 3ml water swallowing with three oro-pharyngeal tasks: i) “prepare to swallow” task to represent pre-oral phase ii) a tongue tap task to represent the oral phase and iii) a throat clear task to represent the pharyngeal phase. The study involved ten healthy young adults and a detailed justification of imaging techniques were provided

(Malandraki et al., 2009). Primary sensorimotor areas were consistently activated during water swallowing as well as all three oro-pharyngeal tasks. Tongue tapping led to more activation in this area than other tasks and the authors speculate increase voluntary motor control requirements for this oral task. The pre-motor cortices are known to contribute to motor planning and execution and again were activated in all tasks. The insular cortices, known for their sensory-motor integration role, while activated in all tasks, were activated more during throat clear suggesting an increased role in laryngeal control. Finally, cerebellum, known for its role in coordination of sensori-motor output was activated during water swallowing but not in the experimental tasks. The authors hypothesise that the cerebellum may be more involved in coordination of the complex sensori-motor tasks of the pharynx rather than simple oral tasks (Malandraki et al., 2009).

Similar findings have been reported in studies using non-imaging methodologies (Huckabee et al., 2003). Using electroencephalography (EEG), Huckabee and colleagues studied pre-motor activation on 20 healthy subjects. They also found consistent supplementary motor cortex activation and concluded that the supplementary motor cortex has a significant role in pre-motor planning and temporal sequencing of volitional swallowing (Huckabee et al., 2003).

Despite bilateral cortical activation, hemispheric dominance for swallowing has been shown and varies from subject to subject irrespective of handedness (Hamdy et al., 2000; Hamdy et al., 1999; Humbert et al., 2009). This may be of interest in dysphagia after cortical stroke. With a significant portion of stroke events in cortical regions rather than the brainstem, the impact of primary sensorimotor damage to all phases of swallowing is of importance.

2.6 Respiration and Airway Protection

A basic understanding of respiration is useful for understanding neurological impairment of swallowing and cough as the systems share common neurophysiological pathways and functions are biomechanically integrated (Martin-Harris, 2008). Respiration is controlled by the inspiratory and expiratory respiratory centres in the dorsomedial medulla, which are associated with the NTS and NA. It is regulated by the pneumotaxic area in the pons (Sawcruk & Mosier, 2001). The sensory receptors involved in respiration are discussed in Chapter Four. Receptors respond to changes in carbon dioxide in the blood as well as other lung changes (Canning, 2006). Sensory information is transmitted through CN X to the NTS and the respiratory centres where respiratory activity is modified (inspiration, expiration, rate and depth of response) through motor pathways to the diaphragm, intercostal muscles, abdominal muscles as well as the larynx (Canning, 2002). During inspiration, the cricothyroid muscles lengthen and tense the vocal cords while the posterior cricoarytenoid muscles increase the diameter of the glottis (Sasaki & Buckwalter, 1984). During expiration, the cricothyroid muscles appear to have a crucial and complex role in airflow control through the glottis (Sasaki & Buckwalter, 1984). As with swallowing, respiratory acts can be consciously altered suggesting a capacity for cortical modulation (Davenport & Reep, 1995). Functional MRI studies report activation in primary motor and supplementary cortices, premotor cortex, insular cortex, basal ganglia, hypothalamus and cerebellum during passive respiration (Davenport & Reep, 1995).

2.6.1 Airway protection.

During swallowing, the airway is protected by closure of the true and false vocal cords, medial movement of the arytenoids towards each other and the downward tilting of the epiglottis (Flaherty, Seltzer, Campbell, Weisskoff, & Gilbert, 1995; Jafari, Prince, Kim,

& Paydarfar, 2003). The larynx moves upward and forward, contributing to pharyngeal shortening, opening of the hypopharynx, inverting of the epiglottis, closure of the airway and opening of the UES (Flaherty et al., 1995; Jafari et al., 2003). Activation of the bilateral thyroarytenoid and cricothyroid muscles as well as the lateral cricoarytenoid muscles and vocalis muscles close the vocal cords (Sasaki & Buckwalter, 1984). The false cords come together when the thyroarytenoid muscles are activated. Extrinsic laryngeal muscles (sternothyroid and thyrohyoid muscles) move the arytenoid cartilages anteriorly and elevate the larynx (Sasaki & Buckwalter, 1984). Impairment to any of these multiple laryngeal muscles groups can lead to aspiration (Cichero & Murdoch, 2006).

It has long been established that the recurrent laryngeal nerve (RLN) provides sensory innervation to the subglottis while the superior laryngeal nerve (SLN) innervates the supraglottis and larynx (Jafari et al., 2003; Sant'Ambrogio, 1996). Numerous studies using internal SLN anaesthesia have established the importance of the sensory function of the internal SLN in swallowing and airway protection (Jafari et al., 2003). Jafari and colleagues conducted a carefully designed study on the effect of internal SLN anaesthesia on swallowing and respiration in humans. Saline control procedures were completed in six subjects and endoscopy confirmed anaesthesia in all subjects. VFSS, airflow measures, respiratory inductance plethysmography and manometry were completed (Jafari et al., 2003). Healthy subjects were able to voluntarily close the airway during internal SLN anaesthesia but regularly penetrated and aspirated despite no abnormal findings in timing or biomechanics in the oro-pharynx on VFSS and manometry (Jafari et al., 2003). In all cases of aspiration, coughing did not occur until the aspirated material reached the trachea again confirming the lack of sensation to the vocal cords (Jafari et al., 2003). They conclude that intact supraglottic sensation is necessary to modulate adequate airway closure during swallowing.

2.6.2 Coordination of swallowing and respiration.

Although efficient, timely transit of the bolus through the oropharynx and adequate airway closure are vitally important, the respiratory system is also crucial to safe swallowing (Cichero & Murdoch, 2006). In normal subjects, there is a consistent respiratory-swallowing pattern emphasising the inter-connections between systems. Swallowing usually occurs after a small inspiration followed by a small exhalation. During the swallow there is a period of apnoea and then after the conclusion of the swallow, there is an immediate exhalation (Preiksaitis & Mills, 1996; Shaker et al., 1992). The period of apnoea occurs during swallowing and facilitates protection of the airway (Hiss, Strauss, Treole, Stuart, & Boutilier, 2003). It usually occurs before the palate is fully raised and precedes laryngeal closure (Hiss et al., 2003). Swallowing apnoea is a protective mechanism and increases in duration with bolus size and with age (Hiss, Treole, & Stuart, 2001; Perlman, Ettema, & Barkmeier, 2000). Respiratory-swallowing coordination is disturbed in neurological disease, with evidence of increased inspiration before and/ or following a swallow (Martin-Harris, 2008). This altered respiratory-swallowing pattern has implications for airway safety. Patients following head and neck cancer treatment, also, have shown the same a tendency to inhale before and/ or after swallowing and this pattern correlates with aspiration and dysphagia severity (Brodsky et al., 2010).

Neural control of the respiratory-swallowing pattern is not well defined. It is thought that there is a close neural relationship between respiratory and swallowing systems in the NTS in the brainstem (McFarland & Tremblay, 2006; Shiba, 2009) and that swallowing neural elements re-task respiratory neural elements to reconfigure the respiratory neural network i.e. reset the respiratory rhythm (Davenport, Bolser, & Morris, 2011). The influence of the cortex on respiratory-swallowing coordination is unclear.

2.7 Summary

In summary, swallowing physiology and airway protection are complex and, although highly reliant on brainstem control, are also dependent on multiple areas of the cortex and subcortex for planning and execution. Respiration is also a cortically modulated act and is intrinsically linked with swallowing and airway protection. Without a clear understanding of respiration and swallowing physiology, assessment and management of patients with swallowing impairment will be sub-optimal.

CHAPTER THREE

DYSPHAGIA

Dysphagia is defined as difficulty with swallowing. Dysphagia is a symptom of a vast number of developmental or acquired disorders and diseases and can occur at any phase of the swallowing process (Cichero & Murdoch, 2006). Dysphagia is common in neurological conditions such as stroke (Daniels & Huckabee, 2008; Mann, Hankey, & Cameron, 2000), progressive neurological diseases such as Parkinson's disease (Johnston, Li, & Castell, 1995) and neurological trauma (E. Ward & Morgan, 2009). Advanced dementia is associated with dysphagia rates as high as 86% (Mitchell et al., 2009). It is a common symptom of structural abnormalities such as head and neck cancer and its treatments, trauma and burns, surgery, tracheostomy as well as medication effects, respiratory disease, infectious disease, autoimmune diseases, gastro-oesophageal conditions and many others (Cichero & Murdoch, 2006). As a symptom of an underlying disease, dysphagia is often described by its clinical signs (coughing, food sticking in the throat, dehydration) and the primary focus of the problem (oral, pharyngeal, oesophageal) (Groher & Crary, 2010). More detailed descriptions of the symptoms (residue in the vallecula, premature spillage to the pyriform fossa) and physiological causes (impaired hyoid movement, reduced base of tongue strength) are commonly used.

Dysphagia after stroke is well documented. Up to 64% of stroke patients are likely to have dysphagia in the acute stages with one study reporting a prevalence of 54% in bilateral hemispheric strokes and 50% prevalence in brainstem strokes (Daniels & Foundas, 1999; Mann et al., 2000). Dysphagia has been associated with increased stroke severity, multiple strokes, reduced level of consciousness, cognitive impairment, aphasia and dysarthria (Baroni, Fabio, & Dantas, 2012; Falsetti et al., 2009; Okubo, Fabio, Domenis, & Takayanagui, 2012). A score of 12 or less on the National Institutes of Health Stroke Scale (NIHSS), an

internationally recognised subjective stroke severity measure, was found to predict dysphagia, as classified by another subjective assessment, the CSE, with 88% sensitivity and 85% specificity (Okubo et al., 2012). In a retrospective study of 378 patients referred for VFSS, those with multiple stroke, brainstem stroke and subcortical stroke had a higher incidence of aspiration than those with cortical stroke (Ding & Logemann, 2000). The most frequent dysphagic impairments on VFSS documented after stroke are delayed swallowing, poor tongue control, weak pharyngeal stripping and poor hyo-laryngeal excursion (Logemann, 1998), with delayed swallowing and decreased hyo-laryngeal elevation the most commonly judged causes of aspiration (Lundy et al., 1999).

3.1 Assessment of Dysphagia

3.1.1 Swallowing assessment.

Dysphagia has been associated with pneumonia and mortality (Barber, Curran, Fishwick, Niimi, & Mishima, 2003; Baroni et al., 2012; WF Westendorp, Nederkoorn, Vermeij, Dijkgraaf, & vandeBeek, 2011), poor functional outcomes (Finlayson et al., 2011; Lakshminarayan et al., 2010), increased length of hospital stay (Altman, Yu, & Schaefer, 2010), dehydration (Crary et al., 2013) and malnutrition (Doggett et al., 2001). These consequences of dysphagia will be discussed in detail later in the chapter. Given the significantly poorer outcomes associated with dysphagia, it is critical that clinicians identify high-risk patients early in their hospitalisation (Perry & Love, 2001). Disappointingly, the New Zealand National Acute Stroke Audit 2009 found only 57% of stroke patients received a swallowing screening prior to commencing oral intake and the report strongly advised that DHBs addressed this with urgency (Stroke Foundation of New Zealand, 2010). Swallowing screening and assessment can take many forms: a checklist of risk factors (Daniels, Lindsay, Ballo, Mahoney, & Foundas, 2000), a water test (DePippo, Holas, & Reding, 1994; Leder,

Suiter, & Green, 2010) or a standardised swallowing assessment including both checklists and oral trials (Ellul & Barar, 1996; McCullough, Rosenbek, Wertz, & McCoy, 2005; Smithard et al., 1998; Trapl et al., 2007). Although the focus of this thesis is on aspiration detection, swallowing assessments clearly have much greater scope in the identification of physiological impairments as well as mealtime competence.

Silent aspiration is difficult to assess at bedside. Asking a patient to cough does not provide information about cough sensitivity only voluntary cough. Absence of cough while drinking or eating also does not reliably indicate absence of aspiration, because the aspiration may be occurring with no response, silently. Validity of the water test has received substantial attention. Its appeal is likely that it is quick and easy to perform. Table 3.1 summarises the results of water swallow tests in predicting aspiration.

Validity varies considerably across studies with the 3oz water test reaching 97% sensitivity in one mixed cohort but only achieving 48% sensitivity in a cohort of stroke patients (McCullough et al., 2005; Suiter & Leder, 2007). Results are difficult to compare. In addition to patient population differences, there are differences in bedside assessment protocols as well as differences in instrumental assessment protocols and definitions of aspiration. Many studies do not disclose whether assessors were blinded to the result of the other test and in the case of the Suiter and Leder study, the same clinician completed the second test immediately after the first adding significant potential for bias (Suiter & Leder, 2007). Studies with time delays between administration of CSE and instrumental assessments in acute, rapidly changing stroke patients should be interpreted with caution. Most importantly, water tests identify patients who cough on aspiration but are limited in their ability to predict silent aspiration. The water test is unlikely to be a reliable tool for identifying patients at risk of silent aspiration.

Table 3.1 A selection of studies demonstrating the range of precision of water tests for predicting aspiration

	Cohort size	*Blinding between assessment results*	*Aetiology*	*Water test*	*Gold standard*	*Delay between tests*	*Sensitivity for predicting aspiration*	*Specificity for predicting aspiration*
Pouderoux, Verdier, and Balmes (2000)	165	Undisclosed	Neuro-muscular disease	Drinking or meals: coughing	VFSS	Undisclosed	75%	69%
Suiter and Leder (2007)	3000	No- same assessor	Mixed aetiology	3oz water: inability to drink, coughing or wet voice	FEES	Water test immediately following FEES	96.5%	48.7%
Nishiwaki et al. (2005)	61	Undisclosed	Acute stroke	3oz water test: coughing or wet voice	VFSS	VFSS within 7 days of water test	72%	67%
Logemann, Veis, and Colangelo (1999)	200	Yes	Mixed aetiology	Oral trial: throat clearing or coughing (part of 28-point screening test)	VFSS	Within 1 day	78%	58%

Mari, Matei, and Gabriella-Ceravolo (1997)	93	Undisclosed	Neuro-logical disease	3oz water test: coughing or wet voice (part of 25-item screening test)	VFSS	VFSS within 72-hours of water test	74%	71%
McCullough et al. (2005)	165	Yes	Acute stroke	3oz water test: coughing or wet voice (part of CSE)	VFSS	VFSS within 24-hours of CSE	48%	95%
				10ml water test: coughing or wet voice (part of CSE)			38%	96%
Rosenbek, McCullough, and Wertz (2004)	60	Yes	Acute stroke	3oz water test: coughing or wet voice (part of CSE)	VFSS	VFSS within 24-hours of CSE	86%	50%
Daniels et al. (1998)	55	Yes	Acute stroke	Progressive water test (5-70ml): coughing (part of CSE)	VFSS	VFSS within 5 days of CSE	57%	85%

The reliability of identifying aspiration in a comprehensive CSE is also poor with most studies indicating that the CSE underestimates aspiration, again due to the presence of silent aspiration (Ramsey, Smithard, & Kalra, 2003; Smithard et al., 1998; Splaingard, Hutchins, Sulton, & Chaudhuri, 1988). By 2012, there were 35 published swallowing assessments according to a recent systematic review (Schepp, Tirschwell, Miller, & Longstreth, 2012). Only four met the authors' basic but unspecified quality criteria for reliability, validity and ease-of-use: the Barnes Jewish Hospital Stroke Dysphagia Screen, the Modified Mann Assessment of Swallowing Ability, Emergency Physician Swallowing Screening and the Toronto Bedside Swallowing Screening Test. A systematic review in 2003 found a wide range of values for sensitivity (42%-92%) and specificity (59%-91%) for identifying aspiration through bedside tests of swallowing (Ramsey et al., 2003). Inter-rater reliability was also variable ($\kappa = 0$ to 1.0) (Ramsey et al., 2003).

Terre and Mearin compared CSE findings with VFSS findings in 64 patients with clinically suspected dysphagia after stroke. They found no statistically significant correlation between CSE results and aspiration on VFSS (Terre & Mearin, 2006). The CSE used was far from comprehensive, consisting of an assessment of palatal and gag reflexes, followed by a judgement of coughing and voice quality changes during thickened fluid intake. The experience and training of the assessors was not described nor was the timing of CSE compared to VFSS. Similarly, Splaingard and colleagues compared CSE findings of 107 mixed aetiology inpatients with VFSS findings performed within 72 hours of CSE. Standardised protocols were used for both assessments and clinicians who completed the VFSSs were blinded to the results of the CSE. They found that 40% of their subjects aspirated (20% silently) with the CSE only identifying 42% of the aspirating patients. Seventy percent of patients with profound aspiration on VFSS were not identified as aspirating during their CSE (Splaingard et al., 1988). The 72-hour time period between

studies leads to concern in an acute population where patients' clinical manifestations can change rapidly. However, the VFSS always occurred after the CSE and thus if swallowing had improved during the time lag, the CSE should have over-predicted aspiration rather than under-predicted it.

Daniels and colleagues have contributed significantly to our understanding of the clinical predictors for aspiration. They completed a number of studies looking at the clinical characteristics and outcomes for patients with dysphagia after stroke (Daniels et al., 1998; Daniels et al., 2000). Swallowing was assessed by CSE and VFSS and they found six predictors of aspiration risk that can be identified at bedside: dysphonia, dysarthria, abnormal gag, abnormal volitional cough, coughing after drinking, voice changes after drinking (Daniels et al., 1998). Although sensitivity and specificity of coughing on water was not substantial (sensitivity 57%, specificity 85%), they demonstrate that combining clinical features provides stronger predictive values. Combining abnormal volitional cough with coughing when swallowing provided 69.9% sensitivity and 84.4% specificity for predicting aspiration (Daniels et al., 2000). The literature to date suggests that no one clinical sign in isolation will provide both high sensitivity and specificity values and that the clinician needs to synthesise a large number of factors in clinical decision-making. However, the significant flaw in even the most comprehensive clinical swallowing assessments is still the absence of a test of airway responsiveness. If a patient does not cough, there is no distinction between those who aspirate silently and those who do not aspirated.

3.1.2 Instrumental assessments.

Considering the poor identification of silent aspiration on clinical assessment, Ding and Logemann strongly criticise the lack of instrumental assessment use in dysphagia following stroke (Ding & Logemann, 2000). Until a reliable, valid bedside assessment of

aspiration is established, instrumental assessments of swallowing such as VFSS or FEES are the only reliable way to identify silent aspiration. VFSS and FEES are both established instrumental tools for identifying normal and abnormal swallowing physiology and identifying presence and absence of aspiration (Langmore, Schatz, & Olson, 1991; Leder, Sasaki, & Burrell, 1998; Logemann, 1998; Wu, Hsiao, Chen, Chang, & Lee, 1996).

VFSS is a multidisciplinary dynamic radiographic study performed in a radiology suite. Patients ingest food and fluids containing radio-opaque barium and the procedure is usually recorded and played back for analysis (Carrau & Murry, 1999). VFSS has the advantage of allowing lateral and anterior-posterior views of the oral, pharyngeal and oesophageal phases of swallowing as well as the airway (Logemann, 1998). FEES, in comparison, is a procedure where a flexible endoscope with a camera and light source is passed through the nose into the pharynx allowing a view of the pharynx and airway while a patient is instructed to eat and drink (Logemann, 1998). The procedure is regarded as safe and is easy to perform at a patient's bedside but like VFSS requires specialist equipment and staff (Warnecke et al., 2009). Again the procedure is usually recorded for later analysis. It has the advantage of avoiding radiation and provides a direct view and access to the vocal cords, airway and the accumulation of secretions (Murray, Langmore, Ginsberg, & Dostie, 1996). However the camera view is obliterated mid-swallow as the scope is covered and FEES provides less information about the oral phase of swallowing, hyoid movement, the UES and oesophagus when compared with VFSS (Aviv, 2000; Logemann, Rademaker, Pauloski, Ohmae, & Kahrilas, 1998) (Figure 3.1).

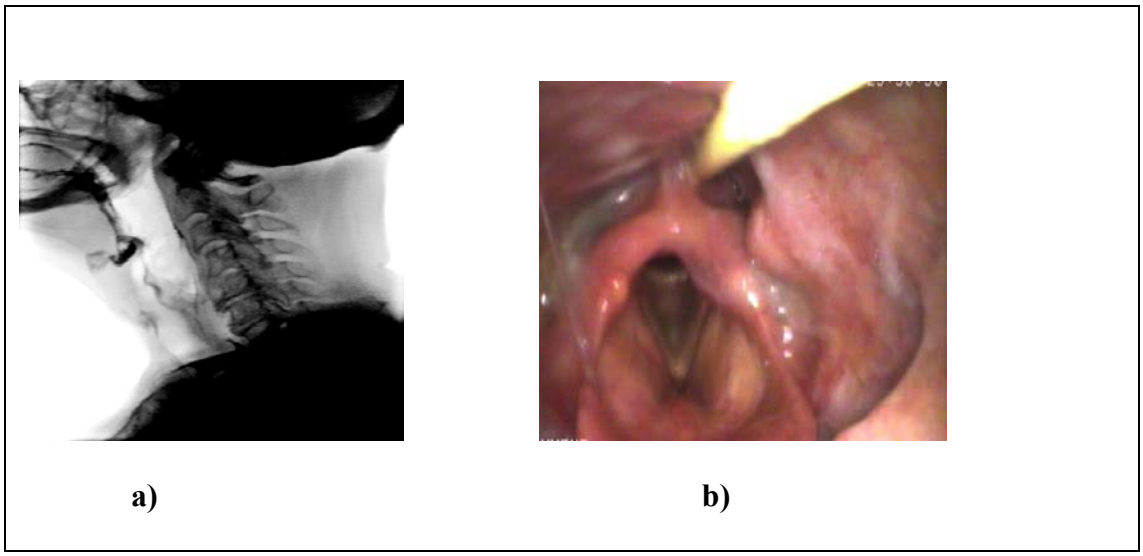

Figure 3.1 Comparison of views seen on a) VFSS vs. b) FEES

Although both assessments are established tools in dysphagia management, they have been criticised for their subjectivity and insufficient reliability (McCullough et al., 2001; Scott, Perry, & Bench, 1998). Fortunately, there is a growing interest in the development of more objective protocols (Leonard & Kendall, 2008; Martin-Harris et al., 2008; Murray et al., 1996). Rosenbek and colleagues have developed strong reliability evidence ($\kappa = .96$) within their research laboratory for their 8-point scale: the Penetration-Aspiration Scale (PAS) (Figure 3.2) (Rosenbek et al., 1996). It can be used in both VFSS and FEES procedures for defining airway invasion and response and encourages more standardised reports of penetration and aspiration (Colodny, 2002; Rosenbek et al., 1996). This scale is widely used in clinical practice and research but has some limitations. It has been published as a scale with progressing severity marked by increasing scores, but this classification is arguable. It relies on depth of aspiration as the primary marker of severity so although a score of five may well be one step more severe than a score of four, the same degree of difference is not as clear for a score of three compared with a score of four where the aspirated material is still

present and risks entering deeper in the airway after the assessment concludes. In fact even an ordinal scale could be argued, as it does not consider silent aspiration (depicted by scores 5 and 8) as more severe than aspiration events where the aspirated material is ejected (depicted by scores 4 and 6). Consequentially, parametric statistical methods have often been used in research using this scale. Yet non-parametric analysis for nominal data may be more appropriate. In research identifying silent aspiration, this internationally recognised scale may not be ideal.

8-Point Penetration-Aspiration Scale

Score. Description of events.

1. Material does not enter airway
2. Material enters the airway, remains above the vocal folds, and is ejected from the airway.
3. Material enters the airway, remains above the vocal folds, and is not ejected from the airway.
4 Material enters the airway, contacts the vocal folds, and is ejected from the airway.
5. Material enters the airway, contacts the vocal folds, and is not ejected from the airway.
6. Material enters the airway, passes below the vocal folds, and is ejected into the larynx or out of the airway.
7. Material enters the airway, passes below the vocal folds, and is not ejected from the trachea despite effort.
8. Material enters the airway, passes below the vocal folds, and no effort is made to eject

Figure 3.2 Penetration-Aspiration Scale scores (Adapted from Rosenbek et al., 1996, p. 94)

FEES is thought to identify small amounts of penetration and aspiration that are not visible on VFSS. Although whether this penetration is clinically significant is questionable as trace penetration and aspiration is relatively common in healthy individuals of all ages (Allen,

White, Leonard, & Belafsky, 2010; Butler, Stuart, Markley, & Rees, 2009). Kelly and colleagues found significantly higher penetration-aspiration scale scores using FEES compared with VFSS in a study using simultaneous FEES and VFSS in 15 dysphagic patients (Kelly, Drinnan, & Leslie, 2007). However, this study has limitations that make strong conclusions from these findings difficult. The 15 SLT raters only reached moderate inter-rater reliability (FEES $\kappa = .64$, VFSS $\kappa = .67$) and rater experience also had a significant impact on penetration-aspiration scores with higher scores rated by more experienced SLTs. Most importantly, the mean difference in scale scores between assessment type was 1.15 which may not be clinically significant, especially as the majority of scores were within the penetration section of the scale (scores between 1-3) (Kelly et al., 2007).

It is important to acknowledge that neither VFSS nor FEES directly assesses airway sensitivity. Instead, a clinician must wait for an aspiration event to occur, and then observe the airway response. An adjunct to FEES is fibreoptic endoscopic evaluation of swallowing with sensory testing (FEESST) (Aviv, Kim, Sacco, & Kaplan, 1998; Flaksman et al., 2006; C. Rees, 2006). This direct test of laryngeal sensation uses an air-pulse stimulator to 'puff' air on the mucosa of the vocal cords stimulating an expiratory reflex (ER)/ laryngeal adductor reflex (LAR) (Aviv et al., 1998). The air pulse pressures can be controlled and normative data has been collected allowing objective interpretation (Aviv et al., 1998). The ER can be visualised and a patient can also be asked to "lift your hand when you feel something". The air puff is accompanied by a marked 'clicking noise' and the travelling air (through the sheath on the scope) is felt through the nose as well as on the vocal cords. It is unknown how these factors impact on test reliability. Placebos involving the subject receiving intermittent zero intensity trials have been used to ensure subjects are responding to sensation rather than the noise of the equipment (Aviv, Sacco, Thomson, & Tandon, 1997). Other reported techniques for assessing laryngo-pharyngeal sensation are described by Nishino and

colleagues and include touching the vocal folds with the endoscope tip or injecting a small amount of distilled water into the larynx and watching for an LAR response (Nishino, Tagaito, & Isono, 1996). These latter techniques are simple, binary measures of sensitivity in comparison to the pressure thresholds obtained during FEESST and are thought to hold a higher risk of laryngospasm (Kidder, Langmore, & Martin, 1994).

3.2 Consequences of Dysphagia

According to the National Acute Stroke Services Audit 2009 (Stroke Foundation of New Zealand, 2010), there were approximately 6,000 first ever and 2,000 recurrent strokes in New Zealand in 2009. Stroke is New Zealand's third highest cause of death and the greatest cause of long-term adult disability (Stroke Foundation of New Zealand, 2010). A large recent international review of stroke services found one third of early stroke-related fatalities were caused by modifiable factors such as pneumonia and the authors state that it is the responsibility of stroke units to reduce these statistics (Koennecke et al., 2011). Dysphagia has been associated with poor outcomes (Altman et al., 2010; Barber et al., 2003; Baroni et al., 2012; Crary et al., 2013; Doggett et al., 2001; Finlayson et al., 2011; Lakshminarayan et al., 2010; WF Westendorp et al., 2011). A recent UK study of 2983 patients found longer hospitalisation and higher mortality for patients with dysphagia with the odds ratio for death of 12.5 if dysphagia was present (Guyomard et al., 2009). Most large-scale stroke studies diagnose dysphagia by subjective CSE rather than instrumental assessment for feasibility reasons and this study is no exception. The dysphagia researcher needs to be cautious in the interpretation of these studies and compare them against the smaller, more objective studies for a fuller picture of the consequences of dysphagia. Prevention of the modifiable consequences of dysphagia and stroke needs careful attention.

3.2.1 Aspiration pneumonia.

Aspiration pneumonia is an infectious process caused by the inhalation of oro-pharyngeal secretions that are colonized by pathogenic bacteria (Marik, 2001). There is a high rate of pneumonia in patients with neuropathologies (Marik & Kaplan, 2003; Yamaya, Yanai, Ohrui, Arai, & Sasaki, 2001). Aspiration pneumonia is the leading cause of sickness and death in patients in residential care (Pace & McCullough, 2010) and is common in patients who are tube-fed as well as those on oral diets (Langdon, Lee, & Binns, 2009). A chart review of 441 consecutive patients transferred to a rehabilitation ward found higher risks of aspiration pneumonia for patients with brainstem strokes (10%) compared with cortical strokes (3%) (Teasell, McRae, Marchuk, & Finestone, 1996). Increasing evidence suggests a critical period of central nervous system induced immunosuppression after stroke when patients are at heightened risk of infection (Emsley & Hopkins, 2010; Langdon et al., 2009; Meisel, Schwab, Prass, Meisel, & Dirnagl, 2005). Langmore and colleagues studied 189 inpatients and outpatients at their medical centre using a strict pneumonia diagnosis criteria and instrumental assessment of swallowing. The authors list the following predictors for aspiration pneumonia: dependency for feeding, dependency for oral care, poor dentition, tube feeding, multiple medical diagnosis and medications and smoking. They hypothesise that dysphagia alone may not be sufficient to cause pneumonia (Langmore et al., 1998). This hallmark research has led to a number of studies and reviews on prevention of pneumonia (Echevarria & Schwoebel, 2012; Eisenstadt, 2010; El-Solh, 2011) with some promising results on reducing pneumonia by increasing oral cares (Maarel-Wierink, Vanobbergen, Bronkhorst, Schols, & Baat, 2013; Ozcaka et al., 2012; Watando et al., 2004). Hoffmann and colleagues have conducted one of the larger studies (N:15,335) on risk factors for development of pneumonia after stroke (Hoffmann et al., 2012). The strongest predictors for pneumonia were older age, atrial fibrillation, dysphagia, male

gender and stroke severity (Hoffmann et al., 2012). Again, dysphagia was classified by a more subjective, standardised swallowing screening tool rather than instrumental assessment perhaps weakening the strength of the results.

3.2.2 Aspiration pneumonia and aspiration.

Although the development of pneumonia is multi factorial (Langmore et al., 1998), there is a significant relationship between dysphagia, developing pneumonia and mortality after stroke (Finlayson et al., 2011; Katzan, Cebul, Husak, Dawson, & Baker, 2003; Lundy et al., 1999; Prass, Braun, Dirnagl, Meisel, & Meisel, 2006; Schmidt, Holas, Halvorson, & Reding, 1994). A prospective study of 166 patients receiving VFSS reported incidence of aspiration and correlated aspiration with demographic factors. Five institutions participated in the study but protocols were strictly controlled and data collection sheets were detailed and comprehensive. They found 51% of patients aspirated (53% of these silently) and aspiration was significantly associated with a history of aspiration pneumonia (Lundy et al., 1999). Schmidt and colleagues completed a small retrospective review of the clinical files of 26 patients with aspiration and 33 randomly selected, case-matched, non-aspirating dysphagic controls. They found that the odds ratio of developing pneumonia was 7.6 times greater for those who aspirated during a VFSS and that the odds ratio for death was 9.2 times greater for those who aspirated thickened fluids or solids (Schmidt et al., 1994). In a larger study, Teasell and colleagues found a 20-fold increase in pneumonia rates in 441 rehabilitation patients who aspirated during their VFSS versus those who did not (Teasell et al., 1996). However, this study was also retrospective and only 106 patients received a VFSS; patients who did not receive a VFSS were judged as non-aspirators based on their CSE alone. This could have led to inaccurate results in view of the inadequate reliability of CSE for detecting aspiration (Ramsey et al., 2003).

The normal protective response to aspiration is the cough. A physiological impairment called *silent aspiration* can occur. It is defined as "the occurrence of aspiration before, during or after swallowing in the absence of cough" (Smith-Hammond et al., 2001, p. 504). In a two-year retrospective study of response to aspiration, 1101 patients of mixed aetiology received a VFSS: 469 aspirated (43%) and 276 of these patients aspirated silently (59%) (C. Smith, Logemann, Colangelo, Rademaker, & Pauloski, 1999). In comparison, Lundy and colleagues detected a 51.2% rate of aspiration in their mixed aetiology cohort of 166, of whom 47% silently aspirated (Lundy et al., 1999) and Garon and colleagues viewed 1,000 patients with neuropathologies and noted aspiration in 57%, with 53% of these silently aspirating (Garon, Engle, & Armiston, 1996). When looking exclusively at patients after stroke, Daniels and colleagues identified 38% of their cohort of 55 aspirated, of whom 67% did not produce a cough response (Daniels et al., 1998).

Silent aspiration has been linked with increased prevalence of pneumonia and mortality (Nakagawa et al., 1997; Pikus et al., 2003). Pikus and colleagues retrospectively reviewed 381 VFSS studies from patients of mixed aetiology. VFSS protocols and data collection methods were carefully described. They reported that patients with penetration of the larynx during swallowing as seen on VFSS had a fourfold increased risk of pneumonia. Those with profound aspiration had a tenfold increased risk and those with silent aspiration had a thirteen fold increased risk of pneumonia (Pikus et al., 2003). Interestingly, depth of aspiration into the airway (tracheal vs. bronchial) was not significantly correlated with pneumonia and they concluded that response to aspiration is more critical than depth of aspiration (Pikus et al., 2003). Reducing aspiration and particularly silent aspiration through improved dysphagia assessment and management should therefore have the potential to reduce pneumonia rates.

Given the severity of consequences of pneumonia post stroke, strict international protocols for pneumonia prevention and treatment would be expected. Surprisingly, current international guidelines do not make strong recommendations regarding early medical intervention to prevent infection (Ionita et al., 2011). Nursing shift changes have been associated with increased pneumonia (Jones, Albright, Fossati-Bellani, Siegler, & Martin-Child, 2011). The authors hypothesised that poorer monitoring of early signs of infection and poorer adherence to swallowing protocols during staff handover contributed to the development of pneumonia. In 1999, Alberts and Brass advocated for careful monitoring of signs of infection and early aggressive antibiotic and antipyretic use (Alberts & Brass, 1999). Yet, the impact of prophylactic antibiotics has still not been investigated thoroughly (Ionita et al., 2011). A recent Cochrane review found five, small, randomised control trials (506 patients) reporting the impact of preventive antibiotics on functional outcomes. There was a reduction in infections but not mortality across trials and the authors urge for larger randomised trials (WK Westendorp et al., 2012).

3.3 Relevance of Sensation

Sensory impairment has been associated with aspiration, pneumonia and disease severity and is relevant to the identification of silent aspiration. Kidd and colleagues tested pharyngeal sensation by touching the pharyngeal wall with the tip of an orange stick and found a correlation between reduced pharyngeal sensation and aspiration identified on VFSS with 80% of patients without pharyngeal sensation aspirating (Kidd, Lawson, Nesbitt, and MacMahon, 1993). In people with Parkinson's disease, impaired laryngeal sensation (using FEESST) has been linked with increased dysphagia severity and disease severity (Hammer, 2009; Hammer, Murphy, & Abrams, 2010).

Aviv and colleagues have extensively studied the relationship of aspiration to laryngeal sensation using FEESST (Aviv, 2000; Aviv et al., 1998; Aviv, Martin, Sacco, & Zagar, 1996; Aviv, Martin, Thomson, & Kim, 1999; Aviv et al., 1997; Aviv, Spitzer, & Cohen, 2002). Their FEESST protocol has been published in detail and assessors were blinded to the results of the instrumental swallowing assessments and to the threshold being stimulated to avoid bias. In a study of 122 patients referred for swallowing assessment, they found that patients with dysphagia and an absent LAR aspirated on thin liquids 94% of the time in comparison with those with an intact LAR who only aspirated 17% of the time (Aviv et al., 2002). There was also a significant association between impaired LAR and pharyngeal weakness as tested by FEESST and a *pharyngeal squeeze manoeuvre* which involves asking a patient to make a forced "eee" sound and watching for degree of pharyngeal movement (Aviv et al., 2002). Patients with both pharyngeal motor impairments and laryngeal sensory impairments had significantly greater risks of aspiration than those patients with impaired pharyngeal contraction but normal LAR (Aviv et al., 2002). Parallel findings were found by Setzen and colleagues in a similarly designed study of 204 consecutive patients referred for FEESST. Aspiration occurred in 100% of patients with both laryngeal sensory and pharyngeal motor impairments while an absence of solely laryngopharyngeal sensory impairment led to only 15% chance of aspiration (Setzen et al., 2003).

Aviv and colleagues report increased pneumonia rates in patients post stroke with bilateral laryngopharyngeal sensory impairments (Aviv et al., 1997). In a two-year follow-up study of 20 patients with acute stroke and dysphagia, six developed pneumonia. Ten patients aspirated on VFSS and nine of these patients had bilateral laryngeal sensory deficits on FEESST; only two developed pneumonia. Of the ten patients who did not aspirate on VFSS, five had bilateral sensory deficits on FEESST; four developed

pneumonia. The authors speculate that patients with bilateral sensory deficits who aspirated on VFSS were placed nil-by-mouth while patients with bilateral sensory deficits who did not aspirate were placed on oral diets. The authors concluded that an assessment of sensory integrity (FEESST) provides a better prediction of pneumonia risk than VFSS alone and that bilateral sensory deficits are associated with pneumonia even in the absence of aspiration documented by VFSS. Again FEESST assessors were blinded to threshold being tested throughout the procedure and blinded to the results of the VFSS and 20 matched controls were assessed as a comparison. However the sample size was small and actual management of patients was not carefully recorded or controlled. Strong conclusions regarding the relationship between sensory deficits, aspiration and pneumonia rates and patient management were speculative.

3.4 Prognosis

The prognosis for dysphagia after stroke is thought to be optimistic with the majority of patients managing oral diets safely within the first week (Barer, 1989; Finestone, Woodbury, Foley, Teasell, & Greene-Finestone, 2002). Mann and colleagues followed 128 patients referred to speech-language therapy after stroke. All 128 patients received a CSE and VFSS within seven days of their stroke and 82 (64%) were diagnosed with dysphagia on VFSS. At six months post stroke, 97 of 112 survivors (87%) had returned to their pre-stroke diet. Interestingly, despite these positive functional outcomes, of the 67 patients who received a follow-up VFSS at three months post stroke, 54 of them showed some persistent swallowing impairments despite being back on their pre-stroke diets (Mann, Hankey, & Cameron, 1999). Sensory deficits of delayed swallowing and delayed oral transit were the highest predictors for pneumonia and failure to return to a normal diet (Mann et al., 1999). Ickenstein and colleagues found that aspiration on instrumental assessment within 72 hours

of stroke was associated with poorer prognosis. Out of 114 acute stroke patients, those who aspirated on FEES were 12 times less likely to be orally fed by 90 days (Ickenstein et al., 2012). Whether these functional outcomes are related to cautious management in patients who aspirated on FEES versus true poor recovery cannot to determined.

3.5 Summary

Dysphagia, especially when accompanied by sensory deficits and silent aspiration, is associated with pneumonia and death (WF Westendorp et al., 2011). After stroke, dysphagia is often a transient problem yet it carries an odds ratio of 12.5 for mortality (Guyomard et al., 2009). Knowledge of risk factors and implications of dysphagia and pneumonia are needed to drive thorough assessment and management of dysphagia. Currently CSEs are not reliable at identifying aspiration, primarily because absence of cough does not reliably indicate absence of aspiration, as aspiration may occur silently (Splaingard et al., 1988). Instrumental assessments can reliably identify silent aspiration but, despite their clinical benefits, referral rates are low (Ding & Logemann, 2000). One possible reason for this may be that they hold disadvantages for the acute stroke patient either in radiation exposure, difficulties accessing the equipment for acutely ill patients, expense, availability of equipment and/or lack of expertise. A reliable tool for identifying silent aspiration, or cough responsiveness, in neurological disease would allow early identification of these high-risk patients.

CHAPTER FOUR

COUGH PHYSIOLOGY

There are a number of different airway responses to irritation. Cough reflexes and expiratory reflexes (ERs) both occur in response to acute airway invasion. The cough reflex is a three-phase process: an inspiration, followed by a forceful expiratory effort against a closed glottis, and finally the re-opening of the glottis and fast expiratory airflow (Morice et al., 2007). Unlike the cough reflex, ER, sometimes referred to as laryngeal adductor reflex (LAR), consists of a strong, brisk expiration without an initial inspiration (Korpas & Jakus, 2000; J Widdicombe & Fontana, 2006). ER is often overlooked in cough studies (G Fontana, 2008; J Widdicombe & Fontana, 2006) (Aviv et al., 1999). The absence of an initial inspiration prior to expiration suggests a different afferent pathway to that of a cough reflex (Korpas & Jakus, 2000). The most likely function of ER is the prevention of aspirated material entering the lungs rather than the clearance of mucus and materials from the lungs and bronchus (G Fontana, 2008). This makes it an important consideration in dysphagia research. The ER has been consistently triggered in studies through mechanical stimulation of the medial margin of the vocal folds, injection of distilled water onto the vocal folds (Korpas & Jakus, 2000; Nishino et al., 1996), through electrical stimulation of the superior laryngeal nerve (Ludlow, Schulz, Yamashita, & Deleyianni, 1995) and through acid cough challenges (R. Addington, Stephens, Widdicombe, Anderson, & Rekab, 2003). It should be noted that although ER was visualised in the mechanical and electrical stimulation studies, the acid cough challenge study only implied ER stimulation through measurements of external abdominal oblique latencies (W. Addington et al., 2003). Although its protective function suggests that the ER would be triggered solely in the larynx, Tatar and colleagues (2008) also demonstrated triggering of the ER through mechanical stimulation of the tracheobronchial

tree (Tatar, Hanacek, & Widdicombe, 2008). Addington and colleagues report that the latencies for ER responses are too short to involve C-fibres and that the cough receptor is the likely afferent route (R. Addington et al., 2003). The ER is not depressed by sleep, anesthetic or codeine like the cough reflex (J Widdicombe & Fontana, 2006). In studying the validity of CRT in neurological disease, the difference between attempting to trigger a cough reflex and triggering an ER may therefore be important if the neural pathways are indeed distinct. However in reality, an ER is often followed by a series of coughs and the distinction may not be clinically relevant (W. Addington et al., 2003; Korpas & Jakus, 2000). Addington and colleagues believe ER to be the vital, initial component of cough reflex in response to aspiration in humans rather than a reflex that should be considered in isolation but this has not been proven empirically (W. Addington et al., 2003).

Cough is our primary defense mechanism for airway protection. In humans, not only can a cough be triggered reflexively, it can be suppressed or initiated voluntarily, implying cortical involvement (GA Fontana & Lavorini, 2006). Neurological damage at the level of the brainstem or cortex therefore has the potential to lead to impairments in cough. In order to assess and treat cough in neurological disease, an understanding of its neurophysiology and biomechanics are necessary.

4.1 Airway Sensory Receptors

The cough reflex is triggered by mechanical or chemical irritants which provide sensory information primarily to receptors in the larynx, tracheobronchial tree and proximal gastrointestinal tract (Canning, 2006). Our understanding of the anatomy and physiology of airway receptors comes primarily from animal studies and, although researched over decades, many uncertainties remain. The differences between species and the effects of the

anaesthesia used in some study protocols have led to many conflicting results across studies (Mazzone, 2005). Human cough involves significantly more supramedullary influences than seen in other species and results from animal studies should be translated to human cough with caution (J Widdicombe et al., 2006). In mammals, there are several types of sensory receptors found in the airway. The receptors can be broadly classified as mechanically sensitive receptors [low threshold mechanoreceptors such as slowly adapting receptors (SAR) and rapidly adapting receptors (RAR)] or chemically sensitive receptors (chemoreceptors/ nocioceptors such as C-fibres) (Figure 4.1) (Canning, 2006; Ho, Gu, Lin, & Lee, 2001; Mazzone, 2005; Mokry & Nosalova, 2007). In order to develop an appropriate CRT, an understanding of sensory receptors and their function is beneficial.

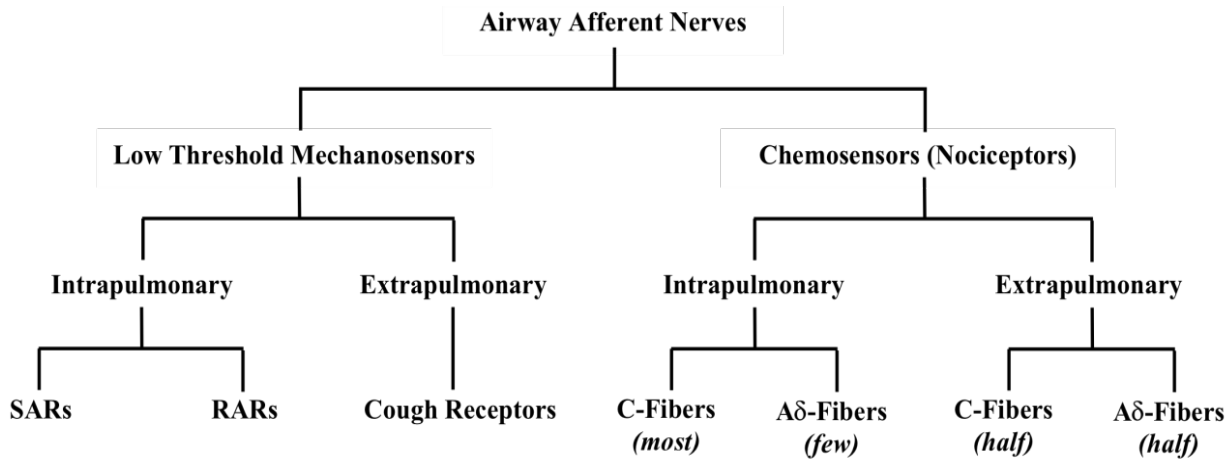

Figure 4.1 Types of airway sensory receptors (Mazzone, 2005, p. 3). Reprinted with permission.

4.2.1 Mechanoreceptors.

Mechanoreceptors, in contrast to chemoreceptors, are activated by mechanical stimuli such as lung inflation and light touch (Mazzone, 2005). The cell bodies are found in the nodose ganglia and project to the airways via RLNs (Canning et al., 2004). Both SARs and RARs are myelinated neurones that appear to have primarily respiratory regulation functions. These receptors have relatively fast conduction velocities compared with other airway receptors (10-20m/sec in guinea pigs). SARs are found primarily in the alveoli and bronchioles and are thought to be responsible for initiation and inhibition of respiration throughout the respiratory cycle, leading to reductions in smooth muscle tone in the airway and reduced phrenic nerve activity. SARs do not respond to chemical stimuli (Canning, Mori, & Mazzone, 2006). As respiratory regulators, it is likely that although SARs may regulate cough pattern, they do not have a primary role in the cough reflex (Canning et al., 2006).

RARs terminate in the epithelium of the intrapulmonary and extrapulmonary airway. These receptors are active throughout normal respiration and respond rapidly to changes in respiratory rate and lung inflation (Canning, 2006; Canning et al., 2006). RARs do not respond to chemical stimuli but do respond to irritants that evoke bronchospasm and obstruction (such as mucus or oedema), e.g., histamine, capsaicin and substance P. Substance P is a sensory neuropeptide found in the epithelium of the airways and when released has an inflammatory effect. It has been linked with submucosal gland secretion, airway smooth muscle contraction and cough production (Sekizawa et al., 1996). Increased substance P has been linked to increased cough sensitivity in patients on angiotensin-converting enzyme (ACE) inhibitors. Substance P levels are lower in patients with advanced Parkinson's disease which is a disease associated with diminished cough (S. Ebihara et al., 2003; Sekizawa et al., 1996). Despite this link to bronchospasm and

substance P, many stimuli activate RARs without resulting in cough. The constant activity of the RARs throughout respiration makes it an unlikely primary receptor for cough and it is thought that RAR activation regulates cough rather than produces it (Canning et al., 2006). There may be situations in which RARs produce cough and these will be discussed in relation to C-fibres in Section 4.2.2.

The extrapulmonary, low threshold mechanosensor, often called the 'cough receptor', appears to serve a different function to other mechanoreceptors (Canning, 2006). Again, cell bodies are found in the nodose ganglia and project to the airways via RLNs and SLNs (Canning et al., 2004). Unlike intrapulmonary RARs, the cough receptor is found primarily within the mucosa of the larynx and trachea as well as, to a lesser degree, the mainstem bronchi (Mazzone, 2005). Although similar to myelinated RARs in many ways, researchers believe this receptor to be unique and the primary receptor responsible for the ER and 'pure' cough reflex, i.e. in response to aspiration or significant irritation (Canning, 2006). It responds to mechanical touch or changes in pH like RARs and is insensitive to capsaicin and hypertonic saline solution (Canning, 2006; Canning et al., 2006; Mazzone, 2005; Stockwell et al., 1993). This receptor does not appear to have a primary respiratory role as it does not respond to smooth muscle contraction or other stimuli known to stimulate RARs and it produces a conduction velocity slower than other mechanoreceptors (up to 5 m/s in guinea pigs) (Canning, 2006). Microinjections of receptor antagonists into a specific point in the NTS (rostal and lateral to obex and commissural subnucleus) abolishes cough but not respiration and RAR or C-fibre activity suggesting a specific site in the NTS for cough alone (Canning, 2008).

4.2.2 Chemoreceptors.

Chemoreceptors are generally activated by chemical stimulation. Seventy-five percent of all airway sensory receptors have been classified as the chemoreceptor, C-fibre, and many researchers have previously hypothesised that C-fibres must play an important role in cough reflex response (Canning, 2006). C-fibres are non-myelinated with a conduction velocity of < 2 m/s in guinea pigs (Canning et al., 2006). These receptors remain inactive during the respiratory cycle and are activated at higher thresholds than RARs and SARs (Ho et al., 2001). C-fibres are thought to have a role in regulating defensive reflexes such as apnoea, bradycardia, and hypotension (Ho et al., 2001). In animals, there appear to be subtypes of C-fibres within the airway (Kollarik, Ru, & Undem, 2007). The majority of C-fibre sensitive neurones innervating the trachea, larynx and lungs have their cell bodies in the jugular ganglia and project to the airways via the SLNs (Canning et al., 2004). These nerves express the neuropeptide, substance P (Canning et al., 2004). Other C-fibres with cell bodies in the nodose ganglia terminate in the lungs only, rarely express substance P and are unlikely to be involved in cough (Canning et al., 2006). In conscious humans, C-fibre activation through chemo-irritants such as capsaicin, bradykinin and citric acid leads to coughing (Canning et al., 2004). However anaesthesia in animals results in immediate cessation of C-fibre-mediated cough while mechanoreceptor cough remains (Canning, 2002; Canning et al., 2004). The need for consciousness perhaps suggests a cortically modulated cough after chemical stimulation rather than a true cough reflex (Mazzone, 2005). Further evidence against C-fibre involvement in cough is that vagal cooling (blocking of the vagal nerve through cooling to 8-10° C) stops coughing but C-fibres remain active (Canning et al., 2004; JG Widdicombe, 1996). Canning describes these findings as evidence that C-fibres are not the primary receptor for cough and

hypothesises that although cough occurs when C-fibres are activated, they are likely dependent on on-going activity from the mechanoreceptor cough (Canning, 2002, 2006). In fact, it has been hypothesised that C-fibre stimulation leads to the release of tachykinins such as substance P that cause airway obstruction or oedema. This oedema results in RAR and cough receptor stimulation and cough (JG Widdicombe, 1996). Evidence for this central interaction between C-fibres and RARs comes again from animal studies. In anaesthetised guinea pigs, capsaicin and bradykinin (chemo-irritants) do not evoke cough but lower the threshold for cough production by electrical stimulation (mechanical stimulation). Microinjections of substance P into the NTS have exactly the same effect on cough induced by electrical (mechanical) stimulation (Mazzone, Mori, & Canning, 2005).

4.2.3 Summary

In summary, the cough receptor is likely primarily responsible for eliciting ER and cough reflex with other receptor types having a modulating role. This cough receptor is found primarily in the larynx and trachea and responds rapidly to touch and pH changes. Cough receptor activation is not hindered by general anaesthetic. Cough receptors can be blocked independently of RAR and C-fibre activity in the NTS resulting in abolished cough but not abolished respiration. Central interactions in the NTS or perhaps cortex may lead to cough induced by chemo-irritants through more indirect routes and account for the role of C-fibres and substance P in cough production. However, the cough receptor is the most likely receptor to respond to aspiration and therefore of great interest to the dysphagia researcher. An understanding of its location and behaviour to different irritants is useful in designing a cough reflex test for dysphagia assessment.

4.2 Sensory Input

Both SLN and RLN carry axons of vagal neurones to the nodose and the jugular ganglia but bilateral severing of the RLN abolishes cough while cough continues despite severing of SLN (Canning et al., 2004). Cough is bilaterally innervated and unilateral severing of the vagus nerve does not affect respiration or coughing (Canning et al., 2004). The cough reflex is threshold-activated with low levels of stimulation triggering receptors but not resulting in a cough (Canning, 2007). At threshold, vagal sensory afferent nerves are activated, sending an excitatory signal through neurones to the nodose and the jugular ganglia and then into the NTS and trigeminal/ paratrigeminal nuclei (Canning et al., 2004; GA Fontana & Lavorini, 2006; Mazzone & Geraghty, 2000; Mazzone et al., 2013). Neurotransmitters are released and act on relay neurones in the brainstem respiratory networks of the ventrolateral medulla [Botzinger and ventral respiratory group (Bot- VRG)] as well as the NTS, midline raphe nuclei, lateral tegmental field, pontine respiratory group (PRG) and cerebellum (Pantaleo, Bongianni, & Mutolo, 2002; Shannon et al., 2004). Motor responses of respiratory reflexes such as ER, apnoeic reflex and cough reflex are produced (GA Fontana & Lavorini, 2006; Vianna, Gilbey, Barnes, Guy, & Gray, 1988).

4.3 Motor Output

To generate an effective cough, muscles of both inspiration and expiration are recruited (GA Fontana & Lavorini, 2006; Gauld, 2009). The respiratory muscles are innervated by a complex combination of thoracic (T1-T12), cervical (Phrenic nerve, C2-C8) and cranial nerves (CN X) (GA Fontana & Lavorini, 2006). Inspiration has a great influence on the intensity of the cough response, i.e. the volume of air inspired relates to the force of the expiration (GA Fontana & Widdicombe, 2007). Inspiration is influenced by contraction of the diaphragm, the intercostal muscles, the accessory muscles

(sternocleidomastoid and scalene muscles) and lengthening of the expiratory muscles (Brooks, 2011; Gauld, 2009; McCool, 2006). The primary expiratory muscles are internal intercostals, oblique muscles, tranversus abdominis and rectus abdominis (GA Fontana & Widdicombe, 2007). The more air that is inhaled, the more lengthening occurs and the higher the intrathoracic pressure (McCool, 2006). During a strong reflexive cough, inhalation can be as much as 50% of vital capacity (between 3-5 litres in an adult), however a cough can be produced by inhaling as little as 50% of tidal volume (approximately 500ml) (McCool, 2006). The closure of the glottis supports the contraction of the expiratory muscles and further builds intrathoracic pressures (McCool, 2006). When the glottis opens, high intrathoracic pressure causes high expiratory flow (McCool, 2006). Power and control is required to ensure the small airways remain patent during the sudden intrathoracic pressure changes (Brooks, 2011; Lasserson et al., 2006).

Laryngeal closure plays an important role in cough efficiency, however a closed glottis is not essential for cough as seen in patients with tracheostomies and laryngectomies (GA Fontana & Widdicombe, 2007). During the inspiratory phase of cough, the laryngeal abductors (posterior cricoarytenoids and cricothyroids) activate and subglottic pressure is low (GA Fontana & Lavorini, 2006; Sant'Ambrogio, Kuna, Vanoye, & Sant-Ambrogio, 1997). During the forceful expiratory phase, the laryngeal adductors (thyroarytenoids and arytenoideus) move rapidly to close the glottis and the abductors relax (GA Fontana & Lavorini, 2006; Sant'Ambrogio et al., 1997) before the posterior cricoarytenoids are finally recruited and adductors inhibited to complete the expiratory forceful movement (GA Fontana & Lavorini, 2006). Experiments have shown the thyroarytenoid muscles to be the fastest to respond to direct recurrent laryngeal nerve stimulation and likely crucial in the ER (Sasaki & Buckwalter, 1984). Impairment to any of these muscle groups or their neural pathways is likely to result in weakened cough and poor airway protection.

4.4 Modulation of Cough

There is evidence of initation of cough or modulation of cough outside of the airway (Widdecombe et al., 2011). Mechanical pharyngeal stimulation results in cough in humans (Nishino, 2000) as does mechanical (distention) and chemical (acid) stimulation of the stomach and oesophagus (Canning & Mazzone, 2003). Researchers hypothesise that oral and nasal sensory receptors also have the potential to influence cough modulation (Widdecombe et al., 2011; Wise, Breslin, & Dalton, 2012). Inflammation and irritation of the nose increases coughing while cold water in the nose and menthol vapours reduce coughing stimulated in the airway (Laude, Morice, & Grattan, 1994; Widdecombe et al., 2011). Likewise, stringent oral cares and capsaicin troche supplements in elderly patients in residental care have both led to increased cough sensitivity (T. Ebihara et al., 2005; Watando et al., 2004). With the closely related sensory and motor pathways of the nose, mouth, pharynx, larynx and oesophagus in swallowing and cough, these influences may well be affected in stroke also. In a patient with neurogenic oropharyngeal dysphagia, can the subtle modulation of cough from the mouth and pharynx be impaired and if so, what impact does this have on swallowing safety?

Although the reflexive cough arc controlled by neurons in the medulla is well established, more recently, evidence has grown in the involvement of cortical pathways in cough. This is crucial to our understanding of cough impairment in cortical stroke. Widdicombe and colleagues propose a model of supramedullary influence on cough (Figure 4.2) (J Widdicombe et al., 2006). This is supported by humans' ability to cough voluntarily and suppress cough as well as the reduction of cough in subjects in coma (Pecova, Javorkova, Kudlicka, & Tatar, 2007; J Widdicombe et al., 2006). It has been postulated that coughing, like swallowing, requires higher brain control of the motor act in response to the sensory

message (Mazzone et al., 2011). In addition to cortical descending pathways modulating the motor response of coughing, higher level sensory pathways also generate the cognitive perception of irritation (Mazzone et al., 2013).

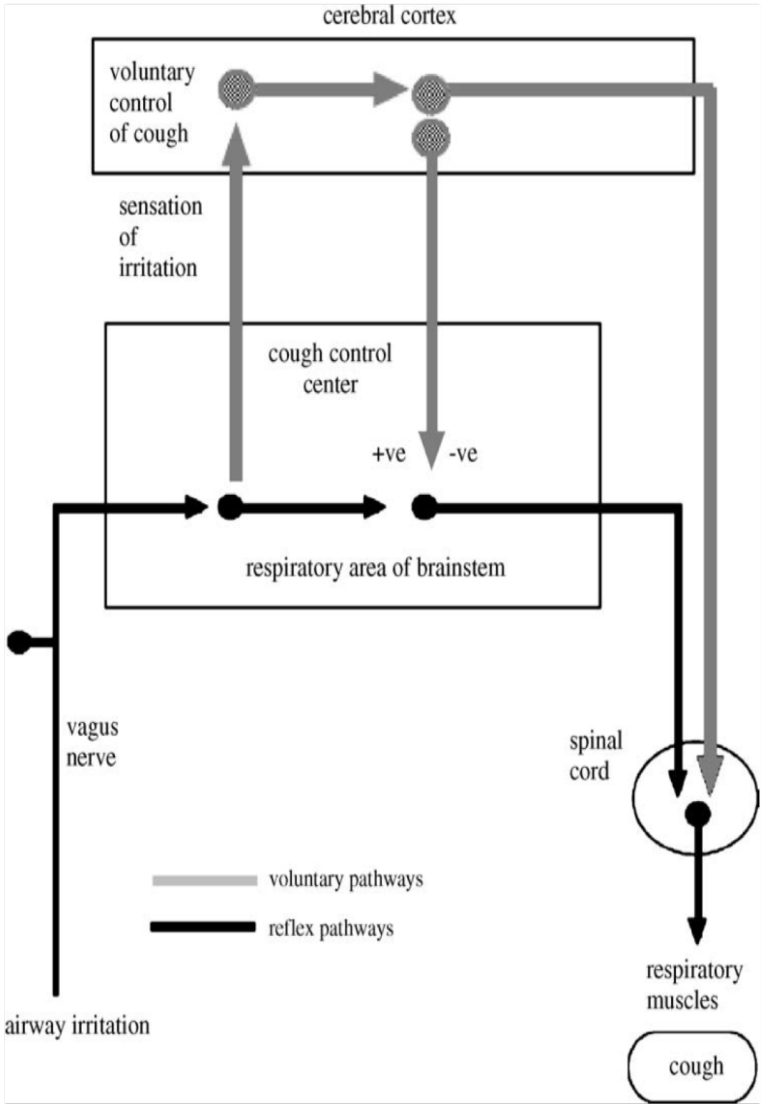

Figure 4.2 Supra-medullary influence on cough (J Widdicombe et al., 2006, p. 323). Reprinted with permission.

Mazzone and colleagues have contributed significantly to the study of neural control of cough. They found cough induced by tussive agent inhalation leads to activation of many cortical and subcortical areas involved in sensory perception, affective processing, motor control and planning. These include the primary motor and somatosensory cortices, supplementary motor cortex, anterior and posterior mid-cingulate cortex, insula, orbitofrontal cortex, thalamus and cerebellum in addition to the brainstem. (Mazzone et al., 2011). Functional MRI studies in cough are plagued with the same methodological complications as those of swallowing. Separating cough related blood oxygen level-dependant (BOLD) responses from other head movements and on-going respiratory and homeostatic acts is problematic (Mazzone et al., 2011). Mazzone and colleagues are explicit in these limitations and describe in detail the filtering approach taken to reduce 'noise.' In a recent study comparing neural activity in evoked cough, suppressed cough and voluntary cough, they found that despite many shared areas of cortical activation, there were unique areas of activation associated with each condition (Figure 4.3). Subjects were provided with visual cues ('go', 'cough', 'no cough') and it is possible that some cortical activation relates to cognitive-language processing. However, unique activations in posterior insula and posterior cingulate cortex were found for evoked cough in comparison to voluntary cough and suppressed cough. Mazzone and colleagues suggest these represent the enhanced motor control of accessory muscles and laryngeal muscles needed in evoked cough tests compared with voluntary cough (Mazzone et al., 2011).

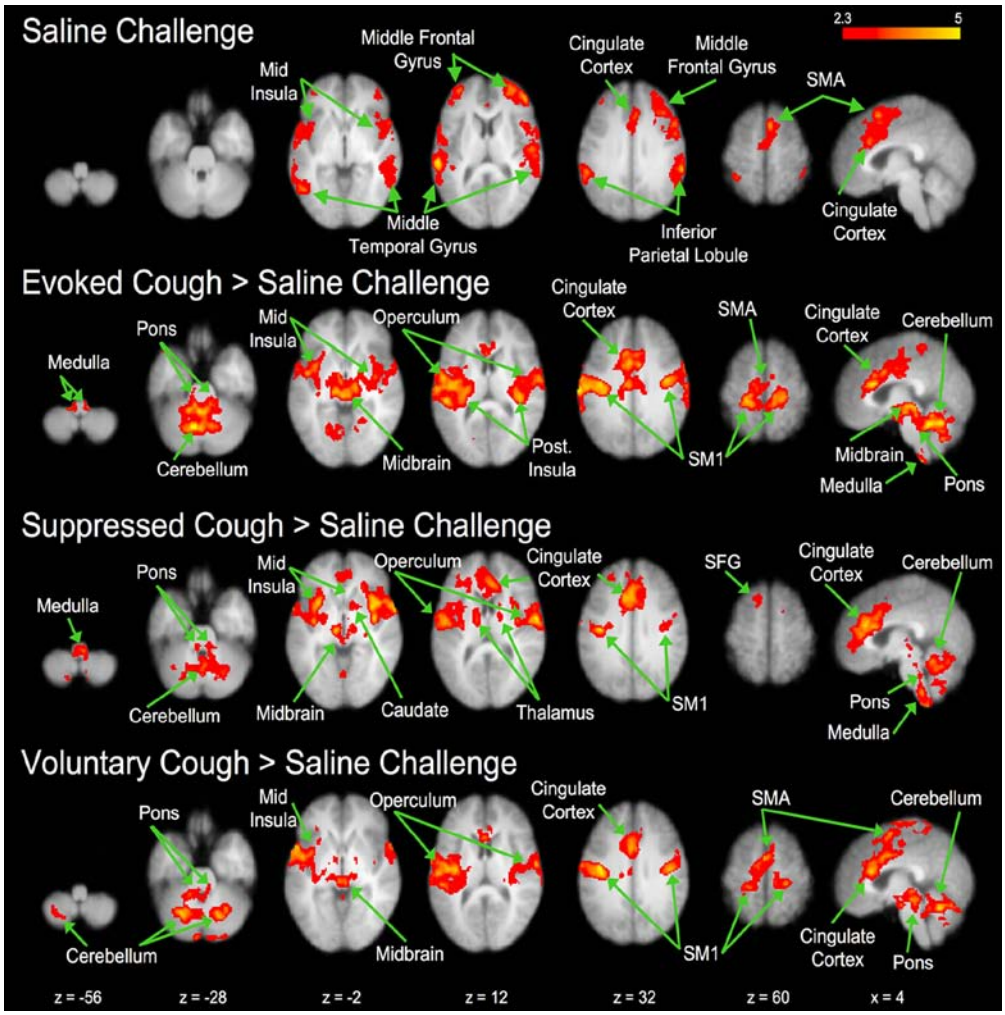

Figure 3. Representative BOLD signal responses associated with saline challenge and evoked cough, suppressed cough or voluntary cough after contrasting activations with saline challenge. The left side of each map corresponds to the left side of the brain. SM1, Primary sensorimotor cortex; SMA, supplementary motor area; SFG, superior frontal gyrus. See Tables 2 and 3 for a list of activated regions.

Figure 4.3 Functional MRI comparing brain activation during reflexive cough, suppressed cough and voluntary cough (Mazzone et al., 2011, p. 2952). Reprinted with permission.

The term *urge-to-cough* has been used to describe the sensation that precedes a sensory-stimulated cough. Mazzone and colleagues describe this as higher level sensory and cognitive processing of airway irritation (Mazzone et al., 2013). Davenport further describes this as a supramedullary brain component of the cough "motivation-to-action system" (Davenport, 2008, p. S107). In certain circumstances, urge-to-cough precedes a motor cough and is triggered at a lower threshold of tussive agent than a cough response. Like a reflexive

cough, the urge-to-cough has a defined threshold and increases as the stimulus increases (Davenport, 2008). A modified Borg scale (1-10; 1= no sensation, 10= maximum urge-to-cough) is the most frequently used measure (Dicpinigatis, Tibb, & Hull, 2011). Interestingly, fMRI has shown capsaicin inhalation evoked urge-to-cough (without coughing) associated with similar motor activations to that of reflexive cough. Additional regions of activation included sensory and cognitive regions such as the primary sensory cortex, supplementary motor area and orbitofrontal cortex (Mazzone, McGovern, Koo, & Farrell, 2009; Mazzone, McLennan, McGovern, Egan, & Farrell, 2007).

Davenport describes the stages for motivation-to-action as: i) the stimulus (ii) the urge to respond (iii) the desire to respond to the urge (iv) the action (v) feedback to the neural system on the action and (vi) the reward, the urge has been satisfied (Davenport, 2008). This model aids our understanding of the human ability to suppress reflexive cough by consciously terminating the process at stage III: Desire for Action (Figure 4.4).

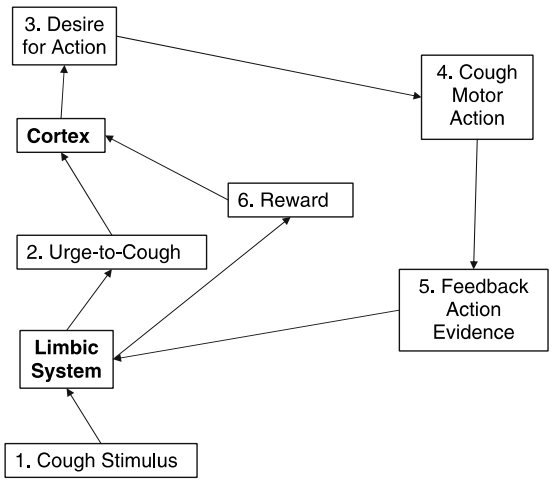

Figure 4.4 Stages of motivation to action of cough (Davenport, 2008, p. S108). Reprinted with permission.

Dicpinigaitis and colleagues have completed the largest evaluation of urge-to-cough to date with 100 participants. They found no gender differences in urge-to-cough, despite gender differences in capsaicin cough reflex test thresholds (Dicpinigatis et al., 2011). Of interest, 21% of subjects did not have a measurable urge-to-cough threshold prior to the cough response, their cough was not perceived as being preceded by an urge. It seems clear that if the stimulus is strong enough, the cough will occur regardless of the desire to suppress it (Dicpinigatis et al., 2011). A study comparing smokers to non-smokers found both decreased cough reflex sensitivity and decreased urge-to-cough in smokers (Kaneszaki et al., 2010). Expanding on this work, another study found immediate increases in number of coughs and urge-to-cough thresholds when nicotine was withdrawn for 12 hours (Davenport, Vovk, Duke, Bolser, & Robertson, 2009). Ebihara and colleagues, using a similar methodology but with citric acid, found that although elderly subjects do not differ in cough reflex threshold in comparison to young subjects, their urge-to-cough was significantly reduced (S. Ebihara et al., 2011). Interestingly, people with congenital central hypoventilation syndrome show the same pattern (Lavorini et al., 2007) and as Ebihara and colleagues ruminate, both population groups are prone to aspiration pneumonia (S. Ebihara et al., 2011). Similar down-regulatory results were found in a study comparing elderly patients with and without aspiration pneumonia. Both heightened cough reflex thresholds and urge-to-cough thresholds were found in those with aspiration pneumonia suggesting a supramedullary dysfunction (Yamanda et al., 2008). Results from urge-to-cough studies are proving reproducible across research groups but the subjectivity of urge-to-cough judgement needs interpretive caution especially in cognitively impaired population groups. This increasing understanding of urge-to-cough may significantly aid our understanding of dystussia and aspiration pneumonia in neurological disease outside of the brainstem. The theory that afferents activate high order cognitive and sensory processes prior to completing the cough

reflex arc holds significant interest for assessment of cough reflex sensitivity in neurological populations. Urge-to-cough measures in cough assessment have potential. In healthy people, low threshold stimuli such as pooling saliva and small amounts of aspiration may often lead to a cortically modulated cough response that begins with an urge. In cortical stroke, this may not be the case. Patients with supramedullary impairment, who perhaps trigger reflexive coughs to large quantities of aspirate or significant irritation may not initiate cortically-modulated coughs to lesser stimuli. If urge-to-cough is impaired, is a higher threshold of irritant required before an ER or cough reflex can be triggered?

4.5 Voluntary Cough

Voluntary cough is also worthy of discussion. Voluntary cough originates in the cerebral cortex and is the purposeful, conscious production of a cough (GA Fontana & Lavorini, 2006; J Widdicombe, Addington, Fontana, & Stephens, 2011). In most cases, except when asked to cough to command, a voluntary cough is still often in response to a sensation of irritation, e.g., during an acute upper respiratory tract infection (Lee, Cotterill-Jones, & Eccles, 2002). Yet, Mazzone and colleagues demonstrate that cortically modulated evoked cough is not simply an urge-to-cough followed by a voluntary cough. Imaging studies of voluntary cough report activation across large parts of cortex and subcortex much like that of reflexive cough (Mazzone et al., 2009; Simonyan, Saad, Loucks, Poletto, & Ludlow, 2007). In contrast, voluntary cough lacks the activation of the posterior insula and posterior cingulate seen in evoked cough tasks and there is a significant scarcity of activation in the lower brainstem (Mazzone et al., 2011). Mazzone and colleagues hypothesised an increased role for the cortex in voluntary cough and suggest

possible cortico-spinal pathway involvement rather than brainstem respiratory circuitry (Mazzone et al., 2013).

Little is known about the pathways between the cortex and brainstem in voluntary cough (GA Fontana & Lavorini, 2006) and separating respiratory activity from cough activity is difficult in fMRI studies. Simonyan and colleagues asked 15 healthy subjects to cough, sniff and breath voluntarily during fMRI (Simonyan et al., 2007). Auditory cues were used with an eight second delayed response to avoid confounding auditory processing activation. Subjects were asked to fixate on a cross in mid-line to reduce extraneous movement. They found similar areas of activation to Mazzone and colleagues. Voluntary cough produced significantly more primary motor cortex, primary somatosensory cortex, and parieto-opercular cortex activation than voluntary breathing. They concluded that voluntary breathing, voluntary cough and sniff all activate similar sensorimotor regions of the brain to different degrees depending on the motor control demands and respiratory-modulation demands of the task. Additional activation was found at the junction of the midbrain and pons during voluntary coughing and the authors postulate a role for this junction in linking the cortex and the cough centres of the brainstem (Simonyan et al., 2007). Functional MRI studies of voluntary cough involve asking a subject to cough to command and results may not translate precisely to voluntary coughing to mild irritation seen in people with a common cold where more sensory interaction may be present.

4.6 Suppressed Cough

With this evidence of complex cortical activation during reflexive as well as voluntary cough, it has been suggested that the addition of a suppressed cough test may represent a more true sensory response in that cortical inhibition can no longer over-ride brainstem responses (Hegland et al., 2012; Monroe, Huckabee, & Robb, 2010). As discussed,

a degree of supramedullary modulation appears to occur during an evoked cough, whilst during a true reflex arc, cortical modulation should not be possible (Hegland et al., 2012). Suppressed CRT thresholds are greater than natural cough thresholds perhaps providing evidence of the supramedullary influence in evoked coughs challenges (Mazzone et al., 2009; Monroe et al., 2010). However, on fMRI suppressed cough appears to activate many of the same regions of the brain as an evoked cough (Mazzone et al., 2011). The only unique activations in the suppressed cough task compared with the evoked cough task were in anterior insula, anterior mid-cingulate cortex, and right inferior frontal gyrus (areas known to be activated during pain stimuli and respiratory suppression) (Mazzone et al., 2011). Hegland and colleagues investigated cough modulation in healthy adults using high concentrations of capsaicin where suppression was not longer possible (Hegland et al., 2012). They asked 20 healthy, young subjects to i) cough smaller/ softer ii) cough longer or iii) not cough. Methods are detailed and carefully controlled and all participants coughed on baseline measures at the supra-threshold capsaicin. They found significant reductions in many components of cough intensity (airflow and sEMG measures) but not in number of coughs produced. Interestingly, a wide range of non-cough respiratory behaviours were noted in participants in the suppressed cough test including breath holding, swallowing, throat clearing and expiratory efforts. They hypothesise that although in the anesthetised patient, a pure brainstem cough may be relevant, in a conscious person even a reflexive cough is likely to involve some cortical modulation (Figure 4.6, revised model of reflexive cough) (Hegland et al., 2012). The impact of age or neurological impairment on this hypothesised model is still unknown. The suggestion is that a suppressed cough task may not, in fact, represent a true cough reflex without supra-medullary influence as previously proposed but instead represents another cough type that is also capable of cortical modulation.

Figure 4.6 Revised model of cortical interaction with reflexive cough (Hegland et al., 2012, p. 45). Reprinted with permission.

4.7 Cough Response to Aspiration

With this substantial history of research in cough physiology and cortical influences, there is surprisingly little research describing either the peripheral or central levels of activity during an aspiration event. Early work by Sant'Ambrogio and colleagues studied laryngeal receptor response to water, dextrose and sodium gluconate in isolated larynges of anaesthetized dogs (Saint'Ambrogio, Anderson, Sant'Ambrigio, & Mathew, 1991). They found randomly active, superficial receptors that responded rapidly to all stimuli and were inactivated by topical lidocaine (Saint'Ambrogio et al., 1991). These receptors fit the

description of ‘cough receptors’ and these results suggest that cough receptors are likely stimulated by aspiration of both water and salty/ sugar solutions.

Thresholds for producing cough in response to aspiration have also not been described. Summation, defined as the increase in sensitivity as the size or duration of stimulation increases, is well documented in skin experiments but little is known about its transference to visceral mechanoreceptors (Gescheider, Guclu, Sexton, Karalunas, & Fontana, 2005; Leder et al., 2010). On the skin, the size of the surface stimulated, the pressure and the duration of exposure all affect the threshold level (Gescheider et al., 2005; B. Green & Craig, 1974; Verrillo, 1966). Hypothetically, larger heavier volumes of aspirated material should lead to greater summation of irritation (by increased surface area and pressure) resulting in a cough response, while smaller quantities might not reach threshold. Sticky, viscous aspirated materials may remain on the vocal cords for longer, again leading to a cough response, while fast moving substances may exit quickly and not reach threshold. This corresponds with evidence that trace penetration and aspiration without a cough response is relatively common in humans (Allen et al., 2010; Butler et al., 2009). As previously discussed, Leder and colleagues studied the diagnostic sensitivity of a large volume water test on cough responsiveness in 4102 patients who received FEES (Leder et al., 2010). Their primary hypothesis was that increased amounts of aspiration would lead to a cough response in patients who may silently aspirate smaller amounts. In their false negative group of patients who passed the large volume water test but were found to silently aspirate on FEES (24/346), one quarter to one third of these patients were classified trace aspirators (Leder et al., 2010). Forty-eight percent (12/25) of patients who silently aspirated on the 10cc of water and 65.5% (21/32) of patients who silently aspirated on puree, audibly aspirated on the larger volume (90cc). This may give strength to the theory that a threshold of stimulation

is required to produce a cough response to aspiration in both healthy and dysphagic individuals, conceivably including those at risk of silent aspiration.

Cough receptors are phasic receptors that are inactive until stimulated and rapidly adapt. These receptors should be vulnerable to adaptation, the phenomenon in which sensory receptors change their sensitivity to a stimulus after prolonged stimulation (Sternberg, 2009). Little has been written about sensory receptor adaptation after prolonged aspiration. Patients with severe dysphagia may aspirate food and drink multiple times per day and may continually have secretions pooled in the upper airways. It is believed that adaptation to mechanical stimuli does not occur until the mechanical stimulus becomes static (Canning, 2011). Although aspiration of food and drink may often be transient as it is either expelled through cough or gradually dispersed lower in the airways, static accumulation of secretions is common in severe dysphagia. Do these patients have neurological sensory impairments preventing them from attempting to clear their airway or, have their sensory receptors adapted to the static stimuli and reduced their sensitivity below the threshold for producing cough? This rapid adaptation of cough receptors has been shown in anaesthetised guinea pigs where a 20-fold increase in acid stimulation had no effect on the number of coughs produced (Canning et al., 2006). However in conscious guinea pigs, C-fibres continued to produce coughs as long as the stimulus was sustained. This suggests that although cough produced via cough receptors adapts rapidly and coughing may halt, chemically irritated C-fibres may continue to fire as long as the irritation continues. This may account for the chronic coughing described in patients with gastro-oesophageal reflux where acid, pepsin and bile may remain in the airway for prolonged periods of time (Canning, 2011). Tachyphylaxis of different tussive agents will be discussed in further detail in Chapter 5.

4.8 Summary

Swallowing and coughing are complex inter-related neural activities. In neurological disease, whether involving the brainstem, sub-cortex or cortex, swallowing impairment is likely to be accompanied by impairments of cough and respiration. Sensory integrity is essential to the entire swallowing process with modulation of motor output in all phases (Steele & Miller, 2010). Afferent information from sensory receptors in the mouth, pharynx, oesophagus and airway modulate multiple components of motor response: mastication, bolus preparation and propulsion, swallowing initiation, airway closure and protection (Steele & Miller, 2010).

Intact sensory pathways are vital for emergency respiratory reflexes during aspiration: ER and cough reflex and therefore impairments in these reflexes carry an increased risk for developing pneumonia (Steele & Miller, 2010). During an aspiration event, aspirated material irritates cough receptors in the larynx and then in the trachea (should the aspirated material descend further). This irritation may lead to high level sensory and cognitive processing. If the irritation is sufficient, an excitatory signal is send through the SLNs (above the vocal cords) and RLNs (below the vocal cords) to the NTS where a motor response is initiated. A rapid ER is initially produced followed, most likely, by a series of cough reflexes. The cortically modulated motor response (number and force of coughs) will depend on the type and quantity of aspirated material.

In designing a cough reflex test for identifying those at risk of silent aspiration, choosing the right ‘cough’ and the right ‘sensory receptor’ to stimulate may be critical. It is important that the researcher understands whether the cough test is assessing cortically modulated cough versus a pure brainstem act as well as triggering cough receptors versus C-fibres. A good understanding of swallowing and cough physiology is vital for comprehensive dysphagia assessment and a well-designed CRT.

CHAPTER FIVE

COUGH TESTING IN DYSPHAGIA

5.1 Cough Reflex Testing Methodology

CRT has been studied in respiratory medicine for more than 50 years. Most frequently it has been used to evaluate the effect of pharmaceuticals on cough sensitivity or in epidemiological surveys (PV Dicpinigaitis, 2007). CRT challenges the sensory integrity of the aerodigestive tract by introducing a tussive agent and observing for a cough response. It therefore has potential as a test of airway sensitivity in dysphagia management. From early in its history, Bickerman stated that in order for CRT to be clinically reliable, the following must be in place: i) there must be a uniform and consistent response in subjects to the same threshold, ii) there must be reproducibility for the same individual, and iii) the method must be non-toxic and simple to administer (Bickerman, Barach, Itkin, & Drimmer, 1954). A clinical guideline on the assessment of cough was produced in 2007 by the ERS Task Force (Morice et al., 2007). It highlighted the continuing lack of standardisation of cough testing despite its longevity. CRT use in dysphagia management requires the same level of reliability, reproducibility, safety and simplicity. Respiratory medicine methodology and experimental findings can serve as useful guidelines for the development of evidence for CRT in dysphagia diagnosis.

Tussive agents most commonly used in CRT include tartaric acid (W. Addington, Stephens, & Gilliland, 1999), capsaicin (Sams, Truncale, & Brooks, 2005; J Smith, Owen, Earis, & Woodcock, 2006), ultrasonic distilled water (GA Fontana, Lavorini, & Pistoles, 2002) and citric acid (Leow, Beckert, Anderson, & Huckabee, 2012; Monroe et al., 2010; Wakasugi et al., 2008) with citric acid and capsaicin by far the most commonly documented. Citric acid inhalation produces a cough through stimulation of both C-fibres

and cough receptors in the larynx, trachea and lungs (Wong, Matap, & Morice, 1999). Citric acid cough is diminished when compared with capsaicin in people after laryngectomy suggesting that citric acid sensitive neurones are more dominant in the larynx and that capsaicin sensitive receptors have a more peripheral distribution (Morice, 1996). However citric acid inhalation leads to cough even when the SLN is anesthetised suggesting that citric acid also stimulates receptors below the glottis (Stockwell et al., 1993). No adverse reactions have been documented in using citric acid in CRT (Bickerman et al., 1954). Of importance, Pecova and colleagues compared citric acid to capsaicin challenges and found fewer healthy participants coughed on the citric acid concentrations. They warn that vital-capacity citric acid challenges may not be ideal when studying decreased cough sensitivity (Pecova et al., 2007).

In comparison, capsaicin is a pungent extract of peppers and induces cough through C-fibre sensory receptors stimulation (Midgren, Hansson, Karlsson, Simonsson, & Persson, 1992; Morice, Kastelik, & Thompson, 2001). Capsaicin has little or no affect on mechanoreceptors (Canning, 2006; Ho et al., 2001; Mazzone, 2005; J Widdicombe, 2001). Capsaicin has also been proven to be a reliable tussive agent and produces no adverse reactions in CRT (Bickerman et al., 1954). Hansson and colleagues studied the difference in cough response to capsaicin between small droplet aerosols that deposit irritant to the lower airways compared with large droplet aerosols that deposit irritant primarily to the larynx. They found far more coughs produced with the small droplet aerosol again suggesting that capsaicin stimulates a more peripheral/ non-laryngeal, rather than laryngeal cough response (Hansson, Wollmer, Dahlback, & Karlsson, 1992).

Tartaric acid, although far less researched, is used by the Addington research group in their work on CRT in dysphagia after stroke and therefore requires mention (R.

Addington et al., 2003; W. Addington, Stephens, & Gilliland, 1999; W. Addington, Stephens, Widdicombe, & Rekab, 2005). Like citric acid, tartaric acid has been used without adverse effect and likely triggers both cough receptors and C-fibres in the larynx (R. Addington et al., 2003). Laryngeal evoked potentials have been recorded in the internal SLN during tartaric acid cough testing and unlike citric acid and capsaicin, tartaric acid cough is abolished or severely diminished by bilateral anaesthesia of internal branch of SLN suggesting primarily laryngeal sensory receptor stimulation (R. Addington, Stephens, Gilliland, & Miller, 1998; W. Addington, Stephens, & Goulding, 1999). This does provide a compelling rationale for its use in the isolated testing of laryngeal sensitivity.

Ultrasonically nebulized distilled water delivers aerolised water to the airways through an ultrasonic nebuliser (PV Dicpinigaitis, 2007). It may be closer in relationship to aspiration of fluids than alternative tussive agents but has limitations. A significant percentage of subjects (15-20%) do not cough at the maximum possible water output from the nebuliser and clinically significant bronchoconstriction has been associated with the test (PV Dicpinigaitis, 2007).

Evidence suggests that these diverse agents stimulate cough through different mechanisms (Midgren et al., 1992). Researchers have found poor correlation between citric acid and capsaicin testing in normal subjects (Midgren et al., 1992; Wong et al., 1999). Midgren and colleagues report two out of three non-responders to citric acid responded to a mild-moderate capsaicin dose while the two low responders to low-moderate capsaicin dose also had a low response to the highest dose of citric acid (Midgren et al., 1992). In contrast, cross tachyphylaxis (blunting of response) does occur when citric acid and capsaicin are administrated in sequence (Morice, Higgins, & Yeo, 1992). Belvisi and Hele, in their review of the literature, found capsaicin more prone to tachyphylaxis and

bronchoconstriction than citric acid with a slower recovery time for capsaicin than citric acid especially after higher doses (Belvisi & Hele, 2006; Morice et al., 1992). Other studies have shown tachyphylaxis after citric acid recovers faster (Morice et al., 1992). In one study evaluating the effect of one-minute of continuous inhalation, citric acid tachyphylaxis occurred within 1-minute and recovery was within 2 hours; while with capsaicin, tachyphylaxis occurred between 1-10 minutes and recovery was slower (still diminished at 3 hours 20 minutes) (Morice et al., 1992). Morice and colleagues hypothesize a different mechanism of adaptation between the tussive agents with the rapid adaptation of extracellular pH the causal factor in the immediate tachyphylaxis and quicker recovery time with citric acid inhalations (see Chapter Four, Section 4.7 for further physiological discussion).

In using CRT in dysphagia assessment, a stable and safe agent is imperative. A consistent response between patients and repeated over time with the same patient is also vital. For the dysphagia researcher, capsaicin may hold less appeal. It is known to prompt longer-term tachyphylaxis than other tussive agents and primarily triggers cough in the lower airways (Hansson et al., 1992; Morice et al., 1992). Citric and tartaric acid have the advantage of stimulating both mechano- and chemo-receptors and are known to stimulate the cough receptors of the larynx, our primary airway protector from aspiration of food and fluids (Morice et al., 2007). Tartaric acid has received less attention and although has the potential advantage of triggering the larynx primarily, little is known about its vulnerability to tachyphylaxis or about the proportion of normal people who do not cough in response to it. Citric acid is unfortunately plagued with a small proportion of non-responders but it does trigger cough receptors in both the larynx and sub-glottis, and tachyphylaxis is quick to recover (Pecova et al., 2007). Although laryngeal sensory receptor activation is important,

response to airway invasion can occur below the glottis and still clear the airway sufficiently. A tussive agent that triggers both the receptors in the supra- and sub-glottis holds merit.

5.1.1 Administration.

There are two common methods of CRT administration: a vital-capacity breath inhalation or a tidal-breath inhalation over a fixed period of time (Morice, 1996). In a vital-capacity breath inhalation, a subject's nose is pinched or clipped and they are asked to exhale, insert a mouthpiece and then take in a deep breath. Nebuliser flow rate is controlled by a dosimeter, often with an inspiratory flow regulator valve. This ensures flow is controlled regardless of the inspiratory effort of the subject (PV Dicpinigaitis, 2007). Any cough response is recorded. In contrast, in a tidal-breathing method, a facemask is placed over the mouth and nose and a prescribed concentration of tussive agent is released from a nebuliser of prescribed flow rate over a prescribed period of time. A nose clip may or may not be utilised. Again, any cough response is recorded. The type of cough triggered by each method has not been investigated. It is possible that the slower tidal-breath method allows more opportunity for cortical modulation than the rapid intake of the vital-capacity method, which perhaps elicits a true ER, followed by a series of cough reflexes. The vital-capacity breath technique requires a subject to follow and perform specific instructions while the tidal breathing method does not require subject instruction compliance. Both of these methods have been used as a single-dose where only one concentration is given or with a dose-response method involving multiple inhalations of different concentrations (Morice, 1996). All methods have proven reliability and reproducibility (PV Dicpinigaitis, 2007; Nejla, Fulimura, & Kamio, 2000). The single-dose method is quick and avoids tachyphylaxis,

whereas more specific information can be derived from cough threshold testing.

Choice of equipment and mode of inhalation has been shown to impact on cough threshold results (Barros, Zammattio, & Rees, 1990; Wright, Jackson, Thompson, & Morice, 2010) and strict methodological control is needed. Drug output rates differ considerably between machines and determine the speed at which a drug is dispersed (Terzano, Petroianni, Parola, & Ricci, 2007). In respiratory medicine, a nebuliser's ability to disperse a treatment quickly with diffuse coverage of lungs is critical (Terzano et al., 2007). Interestingly, significant differences in citric acid cough sensitivity have been reported when nebulisers with different inspiration flow rates are used (Barros et al., 1990). When using a vital-capacity breath inhalation test, Barros and colleagues advise control of nebuliser flow rate (Barros et al., 1990). However they also speculate limitations in the tidal-breath inhalation method where individual respiratory rate may impact on cough response (Barros et al., 1990). Pounsford and Saunders also comment on the effect of individual respiratory rate in tidal-breath inhalations. They caution that irritation and coughing can change an individual's inhalation rate and in turn change the deposition of irritant throughout the test period (Pounsford & Saunders, 1985).

Nebulisers also administer different sizes of aerosol droplets. Particle size appears a crucial factor in determining the specificity of cough challenges with smaller particles better penetrating the peripheral airway (Terzano et al., 2007). Particles of 10 mm diameter are deposited mainly in the mouth and throat, 5-10 mm particles reach the throat and the lungs and particles of less than 5 mm mainly deposit in the lungs (Morice et al., 2001). Capsaicin inhaled in small particle size aerosol droplets at a low flow rate gives a two times larger deposited dose in intrapulmonary airways than fast flow, large droplet aerosols (Hansson et al., 1992). As discussed previously, Hansson and colleagues found four times

higher capsaicin cough sensitivity using the small droplet aerosol technique highlighting the greater presence of C-fibres in the lower airways (Hansson et al., 1992). Notably, for CRT in dysphagia assessment, deposition to the larynx did not differ between methods.

The ERS guidelines recommend standardised use of the same nebuliser for all challenges, preferably a compressed air-driven nebuliser with a flow-limited dosimeter to control flow output regardless of patient inspiratory effort. However, a recent study found different yet correlating thresholds, and strong reproducibility for a simple hand-held nebuliser in comparison to the more conventional compressed air-driven nebuliser with a dosimeter (Barber et al., 2004). The issue may therefore be more about the ability to compare studies that use different methods rather than the reproducibility of each individual method. In CRT, when primarily interested in central laryngeal receptor stimulation and less interested in diffuse peripheral dispersion, the effect of nebuliser type is less clear and needs further investigation.

5.1.2 Delivery method.

Delivery method choice varies between studies and also impacts on the deposition of vaporised particles. A common method for vital-capacity tests is a mouthpiece and an expiration-inspiration method which requires the subject to exhale and then deeply inhale through the mouthpiece with the nose occluded (W. Addington, Stephens, & Gilliland, 1999; Leow et al., 2012). This is the recommended method by the ERC task force for most CRT situations (Morice et al., 2007). In the acute neurological population however, where co-existing impairments of cognition, language, apraxia or oro-motor weakness (i.e. lip seal) are present, this method may not be effective. A more applicable delivery method for

the neurological population may be the passive tidal-breath facemask method (Monroe et al., 2010; Wakasugi et al., 2008). Breathing through the mouth with a mouth piece deposits more particles in the lower respiratory tract compared with nasal breathing and mouth breathing without a tube (Wolfsdorf, Swift, & Avery, 1969). The facemask approach leads to nose and mouth breathing and therefore, perhaps conveniently for dysphagia assessment, deposition of particles to the larynx rather than lower airway.

5.1.3 Methodological issues.

A number of other methodological issues are worthy of discussion and control in CRT research and clinical practice: within subject test variability, suppression/learning effect and tachyphylaxis/ progressive test effect. The number of coughs produced on each trial has been shown to be variable and repeating each concentration a number of times is recommended to obtain the true cough frequency (Morice, 1996). From early in citric acid CRT research, within subject variability has been reported but rarely more than one dose above or below that subject's determined threshold (Bickerman, German, Cohen, & Itkin, 1957). Up to 10% of normal controls fail to cough on maximum doses of both citric acid and capsaicin in vital capacity breath experiments (Morice et al., 1992) though this does not appear to occur as frequently with the tidal breathing method (Barber et al., 2003; Fujimura et al., 1996; Monroe, Manco, & Huckabee, in preparation). Diurnal variability of cough sensitivity is a confounding issue with significantly decreased sensitivity throughout the day (Pounsford & Saunders, 1985). It is usually controlled in clinical trials by testing at the same time each day and if controlled, within subject threshold stability has been shown (P. Rees & Clark, 1983). However this has feasibility issues for acute diagnostic testing within a clinical environment and especially with repeat testing over time. At this point, no

research has attempted re-testing of patients with dysphagia over time and the effect of diurnal variation on this clinical population has not been addressed. In a vulnerable population with decreased airway sensitivity, it is unknown if diurnal changes become clinically relevant.

Cough can be consciously suppressed and suppression is a natural response to the learning effect of irritation and subsequent coughing during cough testing (Bickerman et al., 1954; Midgren et al., 1992). To test for voluntary suppression and to increase challenge blindness the use of placebo inhalations has been encouraged (PV Dicpinigaitis, 2007; Morice, 1996; Morice et al., 2007). When attempting to assess natural reflexive cough, instructing participants to avoid suppressing the cough may be wise.

Short-term tachyphylaxis is well documented in both citric acid and capsaicin cough testing when multiple inhalations over short periods of time are performed (Morice et al., 1992). Randomised concentration administration, although a preferable option for blindness, is prone to short-term tachyphylaxis and blunting of lower concentrations (Morice, 1996; P. Rees & Clark, 1983). Incremental concentration administration interspersed with placebo saline inhalations and one-minute intervals is recommended (Morice et al., 2007). Long-term tachyphylaxis is also reported as much as one week after testing in capsaicin challenges. Morice and colleagues report the most significant adaption effect occurs between test one and two and recommend in research that all participants are accustomed with cough testing before measures are taken (Hoffmeyer et al., 2013; Morice et al., 1992).

5.1.4 Cough recording.

A variety of methods for recording cough response have been used previously. Methods include monitoring of chest movement and acoustic response via phonometer or audiovisual equipment or through pneumotachograph readings (Leow et al., 2012; Lin, Lai, Wu, Wang, & Wang, 1999; Nakajoh et al., 2000). Most clinical studies however simply count the number of coughs produced over the number of trials (Monroe et al., 2010; Wakasugi et al., 2008) and set a criteria for abnormal versus normal response (e.g., 5 coughs = passed test). The ERS Task Force recommend either the use of C2 (2 coughs within 15 seconds of tussive stimuli) or C5 (5 coughs within 15 seconds of tussive agent stimuli) methods as reliable measures of cough response (Morice et al., 2007). Cough resulting from capsaicin and citric acid is usually immediate and counting only the number of coughs occurring in the initial 15 seconds after inhalation is strongly recommended (PV Dicpinigaitis, 2007).

5.2 Influences on Cough Sensitivity

5.2.1 Population variation on cough sensitivity.

There is variation in cough response to irritant across the healthy population (Morice, 1996). This needs consideration when using CRT diagnostically. Cough sensitivity appears to be weaker in premature infants (AB Chang & Widdicombe, 2007). It strengthens through childhood although children appear to have a more sensitive cough reflex than adults (A Chang, Phelan, Sawyer, Del-Brocco, & Robertson, 1996; AB Chang & Widdicombe, 2007). Natural cough thresholds in adults do not appear to change with advancing age (AB Chang & Widdicombe, 2007; Fujimura et al., 1996; Katsumata, Sekizawa, Ebihara, & Sasaki, 1995; Leow et al., 2012; Sams et al., 2005) though older people have shown lower thresholds on suppressed cough testing (Leow et al., 2012). Interestingly, Aviv and colleagues report

significantly diminished laryngo-pharyngeal sensitivity using FEESST with increasing age (Aviv, Martin, & Jones, 1994). Young subjects between 20-40 years old had a mean threshold of 2.07mmHg ± 0.20 and subjects over 61 years old had a mean threshold of 2.68mmHg ± 0.63 ($p < .001$). However, these may not be clinically significant differences as all thresholds sit well within the authors' classification of normal (< 4mmHg). No ethnicity differences have been reported (P Dicpinigaitis, Allusson, Balanti, & Nalamati, 2001) but women have repeatedly shown lower cough reflex thresholds, more frequent coughing and faster adaption to repeated inhalations than men (Becklake & Kauffmann, 1999; PV Dicpinigaitis & Rauf, 1998; Kastelik et al., 2002; Kelsall, Decalmer, McGuinness, Woodcock, & Smith, 2008; Morice, Kastelic, & Thompson, 2000; Rostami-Hodjegan, Abdul-Manap, Wright, Tucker, & Morice, 2001).

5.2.1.2 Normative data.

Until recently, no normative data has been available regarding the normal dosage of tussive agent that should elicit a cough response. Recent research established normative data from a sample of 160 healthy individuals across two studies (Monroe et al., 2010; Monroe et al., in preparation). Studies recruited equal proportions of young and elder (over 65 years) subjects with equal gender representation. In their first study, CRT threshold testing was performed on 80 participants using citric acid and passive respiration through a facemask, incrementally testing from 0.8mol/L up to 2.6mol/L. The majority of participants (95%) produced a natural cough at 0.8mol/L and 68% also demonstrated a suppressed cough (in those patients actively trying not to cough, a cough could be involuntarily evoked) at this level (Monroe et al., 2010). In view of the unfortunate flooring effect at 0.8mol/L, a further 80 participants were recruited and the same CRT protocol was repeated with incremental testing from 0.1mol/L up to 1.2mol/L. Five percent of participants across both studies did not

trigger a natural cough and 22% did not display a suppressed cough threshold at the highest concentration. The mean threshold for producing a natural cough was 0.4mol/L in both young and elder subjects. There was no significant age difference and natural cough was significantly lower than suppressed cough thresholds in both age groups. In line with the literature, females displayed significantly lower mean natural thresholds (female: 0.27mol/L; male: 0.53mol/L) and mean suppressed thresholds (female: 0.35mol/L; male: 0.57mol/L) than males (Monroe et al., in preparation). In using CRT in clinical populations, gender but not age specific thresholds may be advisable. In applying CRT into clinical diagnosis, normative data may not be as important as ascertaining the critical threshold for risk of silent aspiration.

5.2.2 Disease and intervention influences on cough sensitivity.

Activation at the vagal afferent nerve terminals is regulated by both neural and non-neural elements leaving the cough reflex vulnerable to modulation through disease and pharmaceutical interventions (Canning, 2007). As such, cough sensitivity can either increase or decrease and needs attention in patients with dysphagia and when assessing cough reflex for clinical diagnosis and management.

5.2.2.1 Decreased cough sensitivity.

Pharmaceutical agents have been shown to decrease cough reflex sensitivity either centrally or peripherally. Antitussive agents such as codeine (Bickerman et al., 1954; P. Rees & Clark, 1983), opiates (Dilworth, Pounsford, & White, 1990), local anaesthetics such as lignocaine (Hansson, Midgren, & Karlsson, 1994) and antihistamines (Packman, Ciccone, Wilson, & Masurat, 1991; Tanaka, Hirata, Kurihara, Yoshika, & Yakeda, 1996) have all been shown to reduce cough sensitivity and the risks of such drugs should be considered in

managing patients with dysphagia. Decreased cough sensitivity has been found in sleep, coma, increased depth of anesthetic (J Widdicombe et al., 2006), diabetes with autonomic neuropathy (Vianna et al., 1988) and advanced Parkinson's disease (S. Ebihara et al., 2003). This may relate to changes in cortical activation of inhibitory/ suppression pathways of cough and again needs consideration in managing patients with dysphagia (Pecova et al., 2007). For example, CRT may be used in a patient with a reduced level of consciousness but may not be representative of that patient's cough reflex sensitivity once more alert.

Decreased cough sensitivity found in bronchopulmonary diseases such as recurrent pneumonia (Niimi et al., 2003) may relate more to abnormal afferent inputs to the brainstem (Pecova et al., 2007; Yamaya et al., 2001). A small study compared the cough thresholds of seven patients with recurrent pneumonia and no underlying condition to seven controls and found a significant decrease in evoked capsaicin cough sensitivity in the recurrent pneumonia group (Niimi et al., 2003). Recurrent pneumonia was defined by number of previous pneumonias but testing was not conducted until antibiotic treatment for the latest event was completed to avoid the local inflammatory effects of chest infection on cough sensitivity. Whether reduced cough sensitivity leads to pneumonia or whether pneumonia leads to reduced cough sensitivity is unknown. In another small study (N=30) comparing cough reflex thresholds in normal subjects, patients with dementia and patients with aspiration pneumonia, patients with dementia had significantly higher citric acid cough thresholds (37.1±16.7mg/ml) than controls (2.6±0.4mg/ml). Seven out of ten patients with aspiration pneumonia did not trigger a reflexive cough at the highest citric acid concentration used (360mg/ml) (Nakazama, Sekizawa, Ujiie, Sasaki, & Takishima, 1993). Dementia, neurological disease, reduced level of consciousness, multiple medications and recurrent pneumonia are common to patients with dysphagia. Individual variation in cough

sensitivity prevents strong conclusions from these smaller studies but influences on cough from such conditions are highly relevant and needs further investigation.

Dystussia has frequently been identified in the acute stroke population (W. Addington, Stephens, & Gilliland, 1999; Kobayashi, Hoshino, Okayama, Sekizawa, & Sasaki, 1994). Addington and colleagues found 10% of their cohort of 818 patients following stroke failed a tartaric CRT (W. Addington et al., 2005). They hypothesised that the transient or permanent impairment of cough sensitivity, irrespective of the stroke location, relates to what they term 'brainstem shock'. They define this as a global neurological response leading to reduced consciousness, reduced respiratory drive and impaired cough reflex and comment that this needs to be addressed in the acute stages of stroke management (W. Addington et al., 2005). Potentially, in contrast, Smith and Wiles found contradicting results with no impairment in evoked cough sensitivity in 28 patients on a neurological ward. In this pilot study of patients of mixed aetiology, only 13 patients had abnormal swallowing results and neither capsaicin cough thresholds nor numbers of coughs produced were significantly correlated with abnormal swallowing (as defined by speed on a validated water swallow test) (P. Smith & Wiles, 1998). Interestingly, abnormal swallowing was significantly associated with lower maximum inspiratory mouth pressures reflecting either impairments in reflexive cough strength or in patients' ability to achieve an adequate seal of the mouthpiece. However, there are methodological limitations (lack of normal population comparison, lack of diagnostic swallowing assessment, low sample size and wide patient aetiology) but their discussion is worthy of mention. They hypothesise that damage to the corticobulbar pyramidal tract may, in fact, lead to hyper-excitable cough reflexes or reduced voluntary suppression of cough in comparison to damage to the brainstem where the cough centre itself may be impaired (P. Smith & Wiles, 1998). Patient aetiologies in the group classified as dysphagic ranged from encephalitis to motor neurone disease to bilateral partial tenth nerve

palsy making it difficult to speculate the differences between cortical, brainstem and peripheral disease and cough sensitivity. In research looking at cough post stroke, this potential for reduced or perhaps heightened sensitivity needs to be considered. Does the average patient in the acute stages of stroke cough at the same level of tussive agent threshold as normal controls and at what level of difference is this clinically relevant? How long does the cough sensitivity remain reduced? Do some stroke lesions leave patients with hyper-sensitive cough while others lead to dystussia?

5.2.2.2 Heightened cough sensitivity.

Conditions associated with chronic, prolonged coughing lead to increased cough sensitivity in adults and children: gastro-esophageal reflux (Irwin, Madison, & Armando, 2000; Phua, McGarvey, Ngu, & Ing, 2004), allergic rhinitis and atopic dermatitis (Pecova et al., 2007), asthma (A Chang et al., 1996; Koskela, Purokivi, Kontra, Taivainen, & Tukiainen, 2008) and acute viral upper respiratory tract infections (O'Connell 1996). Interestingly cessation in smoking is known to lead to a prompt, temporary enhancement in cough reflex sensitivity (PV Dicpinigaitis, 2007; Sitkauskiene & Dicpinigaitis, 2010). Patients with COPD have heightened cough reflex sensitivity and sensitivity is significantly related to the amount of time they spend coughing (J Smith et al., 2006; JA Smith & Calverley, 2004). ACE inhibiters have been shown to increase cough reflex sensitivity by decreasing substance P catabolism and show promising effects on reducing pneumonia risk after stroke (Arai et al., 2005; Liu, Shau, Wu, & Lai, 2012; Sekizawa et al., 1996; Yamaya et al., 2001). Phua and colleagues found reduced mechanosensitivity (using FEESST) but heightened chemosensitivity (to hydrochloric acid infusion into the pyriform sinus) in patients with gastro-oesophageal reflux disease (Phua, McGarvey, Ngu, & Ing, 2010). They hypothesise

that heightened chemosensitivity is a compensation for the desensitisation of the mechanoreceptors by reflux (Phua et al., 2010).

5.2.3 Summary.

In summary, cough reflex sensitivity is a dynamic phenomenon (PV Dicpinigaitis, 2007; Sitkauskiene & Dicpinigaitis, 2010) with conditions common in patients with dysphagia such as neurological disease, dementia, recurrent pneumonia and multiple medication use associated with diminished cough sensitivity. In contrast, ACE inhibitors and diseases that lead to chronic cough may have the opposite effect and leave a patient with heightened sensitivity (Fox, 1996; Pecova et al., 2007). A comprehensive swallowing assessment should consider each of these potential influences on cough sensitivity when taking a clinical history. Despite these multiple influences on cough sensitivity, it seems likely that there remains a clinically significant cough sensitivity threshold for airway protection and that if a patient's sensory system drops below this point, that silent aspiration may occur.

5.3 Influences on Cough Strength

5.3.1 Disease and intervention influences on cough strength.

Cough strength can be defined as the amplitude of the motor output of coughing either in response to stimulation or under voluntary control. Decreased cough strength leads to a consequent inability to clear material from the airway and therefore likely exacerbates pulmonary sequelae resulting from penetration/aspiration (GA Fontana & Widdicombe, 2007). Both cough sensitivity and cough strength are therefore important to the assessment of dysphagia and an assessment protocol which evaluates both may be advantageous (J Widdicombe et al., 2011).

Diminished cough strength is prevalent in neurological disease including multiple sclerosis (Aiello et al., 2008), Parkinson disease (S. Ebihara et al., 2003; GA Fontana, Pantaleo, Benvenuti, & Gangemi, 1998; Pitts, Bolser, Rosenbek, Trache, & Sapienza, 2008; Pitts et al., 2010) and Duchenne muscular dystrophy (Bach, Ishikawa, & Kim, 1997). It is particularly prevalent in stroke (W. Addington et al., 2005; Smith-Hammond et al., 2001; Stephens, Addington, & Widdicombe, 2003) with up to 78% of patients with acute left middle cerebral artery infarcts presenting with an abnormal voluntary cough (Stephens et al., 2003). Stephens and colleagues collected cough assessment data on 30 patients following stroke: a voluntary cough judgement (normal vs. abnormal) and a CRT result (pass vs. fail on 20% tartaric acid inhalation). All 16 patients with right middle cerebral artery infarcts had normal voluntary cough and reflexive cough results. In the 14 patients with left middle cerebral artery infarcts, 11 had an abnormal voluntary cough with six unable to produce a cough and classified as having cough apraxia (Stephens et al., 2003). There are limitations to this small study. The CRT was a single-dose method limiting the conclusions that a threshold test may have allowed and the voluntary cough judgment was subjective. They also do not report if the six "cough apraxia" patients who were unable to produce a cough to command had been able to follow the instructions to exhale and then inhale deeply required for the CRT.

In a more objective study, Ward and colleagues tested the expiratory muscle integrity of 45 patients following middle cerebral artery ischemic stroke using non-volitional gastric pressure measures to 10^{th} thoracic nerve root stimulation. Twenty healthy controls were assessed for comparison. Methods were tightly controlled with voluntary cough tests completed before CRT to avoid any effects of the tartaric acid and a facemask used to avoid impairments in lip seal influencing results. Their stroke patients had normal gastric pressure measures despite producing weaker reflexive and voluntary coughs (peak

cough flow rate and gastric pressures) compared with controls. They suggest cortical damage impacting on the coordination of activation of the cough muscles in cortical stroke (K. Ward et al., 2010).

In progressive neurological diseases, cough strength reduces with disease progression (S. Ebihara et al., 2003). Fifty percent of patients with multiple sclerosis and 40% of those with Parkinson's disease die from pulmonary complications, with dystussia considered to be a contributing factor (Aiello et al., 2008; Nakashima et al., 1997). In Parkinson's disease, diminished motor cough response appears more problematic than impaired cough sensitivity in the early to middle stages of the disease (S. Ebihara et al., 2003; GA Fontana et al., 1998). Similarly patients with amyotrophic lateral sclerosis often have an intact reflexive cough to stimuli but their cough peak flow becomes so poor that they are unable to clear secretions from the airways (Bach, Bianchi, & Aufiero, 2004). Voluntary and reflexive cough strength measured by internal electromyography (EMG) were assessed in ten subjects with Parkinson's disease and compared with age-matched controls. Diminished expiratory muscle force was found in the patients with Parkinson's disease with reflexive cough strength affected more than voluntary cough (GA Fontana et al., 1998). Like Ward and colleagues, these authors hypothesise that the decrease in EMG activity representing reduced expiratory muscle force is a result of a reduced cortical neural drive (GA Fontana et al., 1998).

The same research group used a similar methodology to study cough in ten laryngectomised patients and ten age-matched controls. Reflexive cough thresholds were calculated at threshold and at supra-threshold using ultrasonic distilled water inhalation with the mouthpiece adapted to tightly cover the stoma in the laryngectomy patients. The authors do not specify that they investigated the impact of these adaptions on flow rate and cough thresholds and these differences in administration between groups may confound

CRT results. Both indirect airflow measures and internal EMG measures were taken to assess cough intensity of voluntary cough, reflexive cough at threshold and reflexive cough at supra-threshold. In the absence of cough threshold differences, they found laryngectomy patients had significantly reduced abdominal muscle contraction and reduced cough peak flow during reflexive coughing at threshold, in comparison to both voluntary cough and reflexive coughing at supra-threshold. The authors' suggest an important role for the larynx in conveying sensory information regarding low intensity irritation and in turn in the regulation of the expiratory muscle pattern (GA Fontana et al., 1999).

5.4 Summary

Despite numerous issues with individual variation and methodology effects, replication of results has been demonstrated across methodologies (Morice et al., 2001). Females have been found to cough at lower concentrations using single dose vital capacity citric acid tests (Thompson, Wright, & Morice, 1999), single dose vital capacity capsaicin tests (Becklake & Kauffmann, 1999; PV Dicpinigaitis & Rauf, 1998) and 15-second tidal breath capsaicin cough challenges (Fujimura et al., 1996). Validation of CRT methodology for dysphagia assessment lags decades behind research motivated by anti-tussive and respiratory interventions. It is likely that some of the methodological differences relevant in respiratory medicine prove irrelevant in dysphagia assessment where focus is transient stimulation of the laryngeal receptors rather than deposition of medication throughout the central and lower airways. Citric acid appears a reasonable choice of tussive agent: i) it produces a cough through stimulation of C-fibres and cough receptors in the larynx, trachea and lungs, ii) but citric acid sensitive neurones are more dominant in the larynx and iii) it is well-established in respiratory medicine as a safe and stable agent. A tidal breath method

may avoid some of the concerns regarding non-respondents and flow rate differences between nebulisers but comes with a risk of variability from individual respiratory rates. A fast flow nebuliser with large particle size droplets is certainly ideal for the upper airway. A facemask not only suits a neurological population but also likely again encourages deposition in the upper airways. In light of the evidence available, tightly controlled protocols are strongly advisable.

Cough sensitivity is altered by a variety of pharmaceuticals and diseases influences. Knowledge of these influences is necessary in the assessment of cough in the dysphagic population. Both cough sensitivity (sensory integrity) and cough strength (motor integrity) are affected in neurological disease, suggesting their importance in dysphagia assessment and management.

5.5 Cough Sensitivity, Dysphagia And Pneumonia

Research has found significant relationships between pneumonia rates and both reduced ER/ LAR (Aviv et al., 1997) and reduced evoked cough sensitivity (W. Addington et al., 2005; Nakajoh et al., 2000; Niimi et al., 2003; Sekizawa, Ujiie, Itabashi, Sasaki, & Takishima, 1990) in patients with and without underlying neurological conditions. Addington and colleagues found a significant relationship between brainstem and cerebral strokes, pneumonia and cough reflex sensitivity (W. Addington et al., 2005). They used tartaric acid with an exhalation-inhalation method using a mouthpiece. They claim that this technique triggers ER followed by a laryngeal cough reflex (LCR). In their 818 stroke patients, 90% of patients had a normal cough reflex and only 3% of this group developed pneumonia. Of the 10% with an abnormal cough reflex, 11% developed pneumonia. The

expiratory-inhalation mouthpiece method is potentially difficult for the neurologically impaired patient. It requires a good lip seal as well as the ability to comprehend and follow motor commands. The authors report that patients who were unable to achieve an adequate lip seal were excluded from analysis, perhaps unfortunately removing more severe strokes from the data pool. Nakajoh and colleagues prospectively studied the incidence of pneumonia in 143 patients over six months post stroke residing in a nursing home facility. They found a significant relationship between pneumonia rates, delayed swallowing response to water injected into the pharynx and cough thresholds with evoked citric acid testing. Patients with lower cough sensitivity and slower swallowing responses were more likely to develop pneumonia. All 14 tube-fed, bedridden patients had slower swallowing responses and none coughed at the highest citric acid concentration (Nakajoh et al., 2000). Unfortunately patients with brainstem strokes were excluded with the rationale that they were already known to be dysphagic and have a risk of pneumonia. Although the swallowing assessment choice was arguably subjective in comparison with an instrumental assessment, the CRT results retain interest in building the argument of this thesis. If cough sensitivity is reduced in neurological disease and is associated with increased risk of pneumonia, the addition of CRT has merit.

5.6 Cough Reflex Testing and Dysphagia

A number of research groups have investigated CRT use in patients with dysphagia. Addington and colleagues studied the addition of a tartaric acid cough challenge to the swallowing assessment of 400 acute stroke patients (W. Addington, Stephens, & Gilliland, 1999). Of 204 participants who did not receive a CRT at a sister hospital, 27 developed pneumonia compared with the 400 participants who received a CRT where only five developed pneumonia ($p < .001$). They utilised a clinical treatment algorithm for oral intake

based on CRT results where a failed cough test resulted in no oral intake and a passed cough test resulted in oral intake. An algorithm with heavy reliance only on cough test findings for decision-making could be perceived as a limitation of this study as clinical management generally incorporates interpretation of other clinical indices. They concluded that an abnormal cough test post stroke indicates higher aspiration pneumonia risk and a normal CRT indicates low aspiration risk (W. Addington, Stephens, & Gilliland, 1999). This study did not justify their dosage of tartaric acid and make no mention of use of normative data trials. Cough sensitivity is highly variable across individuals as discussed previously, and in order for CRT to be clinically valid, a standardised dosage should be used that is based on normative testing. The number of coughs considered to be normal is not reported and 10% of participants were classified as having a weak or absent CRT but definition of 'weak' is not described. The Addington research group used a mouthpiece and the expiration-inspiration method (W. Addington, Stephens, & Gilliland, 1999). As discussed, there are disadvantages to the mouthpiece method in neurological patients. Addington and colleagues state that leakage around the mouthpiece and "puffing" the nebuliser were not considered effective inhalations but do not discuss how many of their acute stroke patients could not perform the task and were therefore excluded from analysis. Exclusion of the more severely impaired patients may have contributed to their low rates of pneumonia.

A more recent study by Wakasugi and colleagues evaluated the validity of CRT using one-minute passive respiration of 1% w/v citric acid via a facemask (with a nose clip), paired with a water swallow test (Wakasugi et al., 2008). Same day videoendoscopy or videofluoroscopy was used to diagnose aspiration risk. When patients with trace silent aspiration were not included as silent aspirators, sensitivity of CRT for detection of aspiration was 89%, specificity was 89%; positive predictive value was 74%, and negative predictive value was 95%. When trace silent aspirators were included as silent aspirators, the sensitivity of

CRT was 67%, specificity was 90%, positive predictive value was 77% and negative predictive value was 84% (Wakasugi et al., 2008). When the aspirators only were analysed and trace silent aspirators were not included as silent aspirators, sensitivity was 87%, specificity was 95%, positive predictive value was 94% and negative predictive value was 88%. When CRT was combined with a water swallow test, 89.1% of those screened as 'normal' were 'normal' on instrumental assessment, 73.7% of those screened as 'aspiration with cough' aspirated and coughed on their instrumental assessment, and 88.2% of those screened as a 'silent aspirator' silently aspirated on their instrumental assessment. (Wakasugi et al., 2008). These results are promising but the justification for dosage of citric acid is not described and is referenced to a Japanese-language journal. Their use of a tidal breathing, facemask method may however ensure patients with poor lip seal, apraxia, cognitive and/or communication difficulties can perform the test.

In 2010, this Japanese research group presented two further studies as posters at the Annual Dysphagia Research Society Meeting. Using their previous citric acid test, they demonstrated in 40 patients, that if the patient coughed at 15-20 seconds, there was 93% sensitivity and 92% specificity for the CRT in identifying silent aspiration. They concluded that 20 seconds of tidal respiration rather than their original 60 seconds was sufficient to detect those at risk of silent aspiration (Takatoshi et al., 2010). They also reported satisfactory reproducibility and reliability with 129 consecutive patients suspected of dysphagia using a 1% w/v citric acid method CRT and a simple hand-held nebuliser in comparison to their original jet nebuliser (sensitivity 88%, specificity 71%, $\kappa = .76$) (Wakasugi et al., 2010). This technique no longer used a facemask and involved a patient inhaling deeply through the mouth (with a nose clip) over a 1-minute period until a cough occurs. Most recently, the same Japanese research group published a prospective validation study of 141 patients using their hand-held mesh nebuliser method (Sato et al., 2012). They found 30 seconds of mist provided

the strongest diagnostic accuracy for detecting silent aspirators from all aspirators (sensitivity 92%, specificity 94%). Sixty seconds of mist provided the strongest diagnostic accuracy for detecting silent aspirators from the full cohort (sensitivity 81%, specificity 65%). Despite these positive findings, limitations in the clinical utility of these results again lie in their failure to adequately justify concentration of tussive agent utilised and the move to a more complex methodological approach for neurological patients (the mouth piece, deep inhalation technique).

Imoto and colleagues attempted to determine the clinically significant cough threshold required to safely commence oral intake in 21 patients with neurogenic dysphagia (Imoto, Kojima, Osawa, Sunaga, & Fujieda, 2011). They used an incremental 15-second capsaicin threshold test followed by 45-second observation periods with a C5 primary end point. They do not discuss whether a facemask or mouthpiece was used or whether passive respiration or the exhalation-inspiration technique was employed. Dysphagia was classified by diet recommendation as mild (full oral intake), moderate (oral intake with supplements) or severe (alternative nutrition) based on videoendoscopy or videofluoroscopy. A significant correlation was found between the grade of dysphagia and the capsaicin threshold value ($p < .001$). Despite significant differences between mean concentrations across groups, the range of capsaicin thresholds within each severity group was extremely wide and overlapped considerably (normal 0.98-7.80, mild 1.95-15.6, moderate 15.6-62.5 and severe 31.2-250). This study lacked the methodological detail required for replication, used sub-optimal dysphagia diagnostics and made arguable conclusions based on the threshold overlaps between groups. Additionally, the researchers' aim to use CRT to accurately assess safety of oral intake appears flawed. CRT assesses only sensory integrity and not dysphagia severity.

5.6.1 Summary.

CRT is not a novel technique and has been extensively researched in respiratory medicine. Strictly controlled methodology is required for CRT to be considered reliable and valid. CRT in dysphagic populations has received much less attention and the range of different methodologies used to date makes comparisons difficult. In using CRT in dysphagia assessment, the choice of tussive agent may be critical and choosing a method closely related to cough evoked by aspiration would be ideal. Promising results from the Addington research group suggest that the addition of CRT to dysphagia assessment could reduce pneumonia rates if the test results are integrated sufficiently into clinical decision-making (W. Addington, Stephens, & Gilliland, 1999). The research from Tokyo also provides promising diagnostic sensitivity of CRT for identifying silent aspirators especially when combined with a water swallow test (Sato et al., 2012; Wakasugi et al., 2008). However, previous research is limited by poor methodological control or reporting. Further research validating a strictly controlled CRT methodology with a justified dosage is warranted.

5.7 Cough Strength, Dysphagia and Pneumonia

Many researchers have investigated the relationship between objective measures of voluntary cough strength, aspiration and pneumonia risk (Pitts et al., 2010; Smith-Hammond et al., 2009). Donha-Schwake and colleagues found inspiratory vital capacity to be the strongest predictor of pneumonia in their paediatric group (Dohna-Schwake, Ragette, Teschler, Voit, & Mellies, 2006). Bianchi and colleagues recently found that patients with dysphagia and pulmonary complications have significantly lower mean cough peak flow values than dysphagic patients without pulmonary complications. They report a cough peak flow of lower than 242 litres/min predicted the development of pneumonia with a

sensitivity of 77% and specificity of 83% (Bianchi, Baiardi, Khirani, & Cantarella, 2012). This was a retrospective study (N: 55) with neurological dysphagia classified by penetration/ aspiration on VFSS and subsequent chest x-ray to examine tracheal aspiration severity. Vital capacity and peak expiratory flow were measured by portable spirometer and there was a 33% pneumonia rate.

Smith-Hammond and colleagues have published various studies correlating abnormal voluntary cough with aspiration risk in dysphagia post-stroke using aerodynamic and sound pressure level measures (Smith-Hammond et al., 2009; Smith-Hammond et al., 2001). Penetration/ aspiration risk was determined using the penetration-aspiration scale on FEES or VFSS. Detailed case histories were taken allowing the researchers to consider the impact of other health conditions and baseline characteristics on cough strength. They discovered that objective measures of cough, such as peak flow of inspiratory phase and expulsive phase and cough volume acceleration, are impaired in patients who aspirate. Although sound pressure levels were lower in aspirators, little difference was shown between mild and severe aspirators, perhaps reducing the clinical utility of objectively assessing loudness/ intensity of volitional cough as part of a CSE (Smith-Hammond et al., 2009; Smith-Hammond et al., 2001). They found that the airflow pattern in aspirating patients was qualitatively different to controls with reduced inspiration and expiration flow rates and longer expulsive phase rise times (Smith-Hammond et al., 2001). Explosive phase rise time was independently associated with aspiration (Smith-Hammond et al., 2001). In a later study, expulsive phase rise time, volume acceleration and expulsive phase peak flow were all found to be sensitive predictors of aspiration risk (sensitivity 91%, 91%, 82% respectively and specificity 81%, 92%, 83% respectively) compared with a bedside water test (sensitivity 39%, specificity 82%) (Smith-Hammond et al., 2009).

In a pilot study, Pitts and colleagues also found a modest relationship between voluntary cough strength (objective airflow measures) and aspiration on VFSS in 20 patients with Parkinson's disease. In a later larger study (N: 58), they found expiratory phase peak flow was significantly associated with aspiration on VFSS (area under the curve (AUC) = .88, sensitivity 57%, specificity 100%) (Pitts et al., 2010). The sample size of this study was small especially as only 5 patients aspirated on VFSS. Further work in this population group is required.

5.8 Cough Strength Testing and Dysphagia

Clinically, it is important to distinguish between cough sensitivity and cough strength as they are different neurophysiological processes and, although deficits in both may lead to an increased risk of pneumonia, assessment and management are significantly different. Objective cough strength measures appear to be strong predictors of aspiration risk and pneumonia but they do not distinguish between the audible aspirator and the silent aspirator and therefore hold a different value to that of cough reflex testing. Objective measures of cough intensity require additional equipment: 'expiratory' EMG, airflow measurements, respiratory pressures, sound pressure measurements and lung volume changes such as use of a pneumotachograph (GA Fontana et al., 1998; GA Fontana & Widdicombe, 2007; Smith-Hammond et al., 2009). Equipment is expensive and cumbersome and requires specialist training. It cannot be taken to the bedside and may be impractical for routine CSE. If a subjective judgement of cough were proven reliable, it would certainly be advantageous.

5.8.1 Subjective cough judgements.

There are differences of opinion among research groups on the adequacy of subjective cough measures, perhaps related to their primary research focuses. Addington and Widdecombe, who have focused their work on the sensory cough pathway, write "a subjective measurement of voluntary cough (VC) has not been shown to give less acceptable results than the objective method" (W. Addington & Widdecombe, 2009, p. 647) but provide no empirical justification for this statement. In contrast, Gauld and colleagues and Smith-Hammond and Goldstein, whose work has focused on the motor cough pathway, write of their opinion that subjective assessment of cough is not accurate or reliable but again do not support this statement with data (Gauld, 2009; Smith-Hammond & Goldstein, 2006).

Objective cough strength measures are not a standard component of a bedside swallowing assessment whereas subjective cough strength judgements are common in clinical practice. However, there is a paucity of research looking specifically at the inter-rater reliability of subjective judgements of either voluntary or reflexive cough. A number of research groups have assessed inter-rater reliability and the studies all investigated the clinical utility of CSE protocols with voluntary cough as one of many measures. Daniels and colleagues evaluated the reliability of clinical swallowing assessment measures, including normal versus abnormal voluntary cough and reported 95% inter-rater agreement for all binary measures (Daniels et al., 1998). In a subsequent publication, they described their definition of abnormal voluntary cough as "a weak response, verbalized response, or no response on [when] given the command to cough" (Daniels et al., 2000, p. 1031). Rater experience or training was not discussed. Rosenbek and colleagues also found acceptable inter-rater reliability (Kappa significant at $p < .005$) between three experienced judges across all aspects of a clinical swallowing evaluation, including voluntary cough strength

(normal vs. abnormal) and quality (wet vs. dry) (Rosenbek et al., 2004). Again they give few details on the training of the clinicians but describe raters as trained to criterion (Rosenbek et al., 2004). In a later study, McCullough and colleagues, again, used only experienced judges who were trained to criterion. In this study, they judged voluntary cough strength (normal vs. abnormal) with 100% agreement, volitional cough quality (wet vs. dry) with 85% agreement, reflexive cough strength (normal vs. abnormal) with 85% agreement and reflexive cough quality (wet vs. dry) with 92% agreement (McCullough et al., 2005). All these studies utilised experienced, trained researchers; they do not provide evidence for the reliability of untrained, inexperienced clinicians.

Smeltzer and colleagues studied the reliability and validity of a cough strength index in people with multiple sclerosis (Smeltzer, Lavietes, Troiano, & Cook, 1989). The index includes a subjective voluntary cough strength rating (1-3) as well as a patient rating of mucus clearance and cough strength ability (Smeltzer et al., 1989). Independent, practising neurologists performed the tests. Their results were positive with high agreement ratings (intra-rater reliability $\kappa = .94$, inter-rater reliability $\kappa = .87$). Sensitivity and specificity of the index for predicting those with a maximum expiratory pressure of < 50% was 81% and 79% respectively (Smeltzer et al., 1989). These data suggest that reliable subjective judgement of cough strength may be possible for patients and independent practising clinicians.

5.8.2 Voluntary cough or reflexive cough strength?

Interestingly, some researchers have warned against the use of voluntary cough strength measures for judging a patient's ability to clear the airway after aspiration of food and/or fluids (W. Addington, Stephens, Phelipa, Widdicombe, & Ockey, 2008). Voluntary and reflexive cough respond differently to disease (GA Fontana et al., 1998; Stephens et al.,

2003; K. Ward et al., 2010). Weakened expiratory cough strength clearly impacts a patient's ability to clear the airway but involuntary reflexive pathways cannot be judged by a voluntary act (W. Addington et al., 2008). Although reflexive cough and voluntary cough are thought to be acoustically the same and both involve the same closed glottis and inspiration/expiration pattern, the motor component of voluntary cough is different to that of a reflexive cough with a suggestion of different underlying neural pathways (Lasserson et al., 2006; Magni, Chellini, Lavorini, Fontana, & Widdicombe, 2011).

Typically a reflexive cough is approximately 80% of the intensity (as seen with expiratory flow rates and abdominal muscle EMG values) of a maximum voluntary cough regardless of the tussive agent used (Magni et al., 2011). Magni and colleagues hypothesize that it is produced consistently at a threshold sufficient to clear the airway (Magni et al., 2011). Lasserson and colleagues studied the differences in motor activity between reflexive cough and voluntary cough in ten normal subjects (Lasserson et al., 2006). In this study, surface EMG and cough flow measures were taken and reflexive cough was evoked by one-minute intervals of passive tartaric acid inhalation through a facemask. Reflexive cough involved simultaneous, rapid and short-lived EMG activity of expiratory and accessory muscles; while during voluntary cough, EMG activity increased gradually starting with expiratory muscles with accessory muscles sequentially becoming involved (Lasserson et al., 2006). The authors acknowledge the limitations of surface EMG accuracy but all subjects were of average size and weight and all measures were taken within the same session.

In a brief report of two healthy subjects, Stephens and colleagues demonstrated a difference in diaphragmatic movement using digital VFSS measurement between reflexive and voluntary cough. An increased upward movement of the diaphragm was seen with reflexive cough in keeping with its vital role in rapid removal of airway threat (Stephens,

2003). Although only two subjects were tested, leading to questions regarding individual variability and statistical significance, the results correspond with other comparable studies. In a later study, intra-abdominal pressures were also found to be different between reflexive and voluntary cough in 11 subjects (W. Addington et al., 2008). Bladder and rectal pressures and urethral EMG were measured using an urodynamic system where a pressure catheter is inserted into the bladder and rectum. All subjects were female to avoid gender differences confounding results; nine subjects were healthy, one subject had multiple sclerosis and one subject had a T_4 spinal cord injury. Protocols were detailed and controlled with instructions to produce a forced exhalation before each CRT to reflect the respiratory pattern of an aspiration event mid-swallow. Reflexive cough intra-abdominal pressures were significantly greater and more prolonged regardless of the duration of the coughing period in comparison to voluntary cough pressures (W. Addington et al., 2008).

Although the term reflexive cough has been used in describing these studies, as discussed previously, Addington and colleagues believe ERs and cough reflexes cannot be separated in an aspiration event where the former always precedes the latter (W. Addington et al., 2003). They define the cough stimulated by their CRT as a series of ERs followed by cough reflexes "involuntary rapid synchronous expiratory muscle activation that causes and sustains an elevated intra-abdominal pressure event over time, sufficient for airway protection following a threatening supraglottic laryngeal stimulus" (W. Addington et al., 2008, p. 9). They therefore discuss that this sustained, increased expiratory power triggered by their tartaric CRT is despite a lack of inspiratory effort (W. Addington et al., 2008). Inspiratory effort has a significant effect on cough strength and is absent in ER. Again, they suggest that this provides evidence for the protective nature of reflexive cough. Widdicombe and colleagues theorise greater neural facilitation leading to more rapid recruitment of muscle activity in the absence of the higher levels of subglottic pressures that

occur with greater inspiratory effort (J Widdicombe et al., 2011). It should be noted that their justification for the trigger of ERs rather than cough reflexes with their CRT is based on clinical experience rather than empirical evidence (W. Addington et al., 2003). Irrespective of this debate, evidence is building for different motor patterns for ER and/or reflexive cough compared with voluntary cough with more rapid neural activation of muscles in the reflexive cough type.

Finally, there are also practical limitations to voluntary cough testing in patients following stroke where level of consciousness, difficulties following instructions and apraxia can making execution difficult (Smith-Hammond et al., 2001). Measures of reflexive cough efficiency may be more feasible and more accurate for identifying at-risk patients for aspiration pneumonia in view of its importance as the initial airway protection mechanism (Magni et al., 2011). Little research has been published on objective or subjective reflexive cough strength.

5.8.3 Summary.

Cough strength testing has significant value in the assessment of a patient with dysphagia. Using objective cough measures, it has been shown that weakened cough is associated with aspiration and pneumonia. Yet, subjective cough judgements have received little investigative attention despite common usage. Assessment of the strength of reflexive cough rather than voluntary cough may prove more valuable in assessing a patient's ability to clear aspirated materials.

CHAPTER SIX

HYPOTHESES

6.1 Study I and II. Validation of CRT against instrumental assessment of aspiration

Research question

There is increasing evidence of the validity of CRT for identifying silent aspiration. Previous research has used sub-optimal methodology for the neurologically impaired patient and has not determined the dosage of tussive agent that best differentiates silent aspirators from audible aspirators and non-aspirators (Section 5.6). The following questions remain under-investigated: can CRT accurately predict patients who silently aspirate and what concentration of citric acid provides the best predictive measure?

Hypotheses

There will be a statistically significant agreement between CRT result and response to aspiration on instrumental assessment. More specifically, patients who fail their CRT will be significantly more likely to silently aspirate on instrumental assessment and patients who pass their CRT will be significantly more likely to cough in response to aspiration on instrumental assessment. There will be differences in sensitivity and specificity values for CRT in predicting silent aspiration at different concentrations of citric acid with high concentrations providing higher specificity values and low concentrations providing higher sensitivity values.

Rationale

Silent aspiration is associated with increased prevalence of pneumonia and is poorly identified by traditional CSE (Section 3.2). CRT provides information about airway

sensitivity and therefore may act as a surrogate for silent aspiration and identify those at most risk of not responding to airway irritation (Section 3.3).

Proposed studies

The aim of these studies was to validate CRT against instrumental observations of aspiration and to determine what concentration of citric acid provides the best predictive measurement of silent aspiration risk. In Study I, 80 patients participated in a single-blinded correlational study. All patients received a cough reflex threshold test and a VFSS. The validity of CRT was evaluated against response to aspiration on VFSS to find the optimal threshold for detecting silent aspiration (Chapter Seven). In Study II, 101 patients participated in a similar single-blinded correlational study but all patients received a FEES as well as a cough reflex threshold test. Again the validity of CRT was evaluated against response to aspiration on FEES to find the optimal threshold for detecting silent aspiration (Chapter Eight).

6.2 Study III. Intra-and inter-rater reliability for judgement of cough following citric acid inhalation

Research question

There is evidence that the motor pathway of reflexive cough differs from that of voluntary cough and that measuring the strength of reflexive cough is more valuable than voluntary cough in judging a patient's ability to protect the airway from aspirated material (Section 5.8). There has been little investigation of the reliability of subjective cough judgements by SLTs (Section 5.8). Can SLTs reliably judge the strength of a patient's cough induced by citric acid inhalation?

Hypothesis

SLTs will achieve a substantial level of intra and inter- agreement ($\kappa = 0.61$- 0.80) when judging the strength of coughs induced by citric acid inhalations (Landis & Koch, 1977).

Rationale

Cough strength, in addition to cough sensitivity, has been linked with increased aspiration and pneumonia risk (Section 5.7). Subjective cough judgement is relatively common in bedside CSE but the reliability of such judgements has not been investigated.

Significance

Objective cough assessment requires expensive, cumbersome equipment and specialised training and is not currently practical for clinical use. If SLTs can reliably make subjective judgements of cough strength, this equipment may not be necessary in the early assessment of cough at bedside.

Proposed study

The aim of this pilot study was to assess the inter- and intra-rater reliability of subjective judgements of cough following citric acid inhalation. Eleven SLTs using CRT clinically and 34 SLTs without CRT experience viewed ten videos of patients coughing following citric acid inhalation. They were asked to judge the cough as strong, weak or absent. They watched the videos twice with a short break between viewings. Inter- and intra-rater reliability was analysed and those with clinical experience of CRT were compared to those without (Chapter Nine).

6.3 Study IV. Inter-rater reliability for judgement of cough following citric acid inhalation following training

Research question

In our earlier study, un-trained SLTs achieved only fair to moderate agreement in judging cough strength (Study III, Chapter Nine). With training, can SLTs reliably judge the strength of a patient's cough induced by citric acid inhalation?

Hypothesis

Specific training in cough physiology and cough strength judgement will lead to substantial agreement ($\kappa = 0.61 – 0.80$) between SLTs in judging the strength of cough induced by citric acid inhalations (Landis & Koch, 1977).

Rationale

Measuring the strength of reflexive cough provides valuable information about a patient's ability to protect the airway from aspirated material (Section 5.7). The reliability of subjective cough judgements by SLTs has received little research attention (Section 5.8). There is minimal formal training of cough physiology in undergraduate SLT programmes and no research on the effect of specific training on cough judgement. Study III found only fair to moderate agreement in untrained SLTs on judging reflexive cough strength (Study III, Chapter Nine).

Significance

If training can lead to substantial agreement between SLTs in cough strength judgements, the inclusion of such training can be incorporated into undergraduate and in-house training and subjective cough strength judgements can be used in clinical practice.

Proposed study

The aim of this study was to assess the effect of specific cough judgement training on the inter-rater reliability of subjective judgements of cough following citric acid inhalation. Fifty-eight SLTs were trained specifically in cough physiology and cough strength judgement. Training included defining a cough from other respiratory responses/acts and judging the strength of a cough. The SLTs then watched ten videos and judged the coughs as i) present or absent and ii) strong or weak. Inter-rater reliability was analysed. Effect of years of experience in dysphagia management and experience in CRT on reliability was assessed (Chapter Ten).

6.4 Study V. Clinical implications of CRT in dysphagia management following stroke: A randomised controlled trial

Research question

There is increasing evidence of the clinical utility of CRT in reducing pneumonia following stroke. However, methodological limitations in previous studies prevent CRT from being easily translated into clinical protocols. Researchers have used sub-optimal methods for the neurologically impaired patient and have not justified dose of tussive agent utilised (Section 5.6). Further investigation is needed to understand: does the inclusion of a

controlled, applicable CRT reduce adverse outcomes for people with dysphagia after stroke?

Hypothesis

The addition of CRT to a standard CSE will result in a statistically significant reduction in pneumonia and mortality rates compared with standard CSE alone.

Rationale

Significant health issues and service delivery costs are associated with post-stroke pneumonia related to dysphagia. Although the development of pneumonia is known to be multi-factorial, silent aspiration (aspiration without a cough response) has been linked to increased prevalence of pneumonia and mortality (Section 3.2). CSE is not, however, able to effectively identify patients who silently aspirate (Section 3.1). CRT provides information about airway sensitivity and therefore may indicate those at most risk of not responding to airway irritation such as silent aspiration (Section 3.3).

Significance

The addition of a validated test of 'silent aspiration risk' will significantly improve clinical assessment of dysphagia. Without a test for silent aspiration, many patients are either not referred to SLT or are managed incorrectly as non-aspirators. If identified early, patients at risk of silent aspiration can be referred for instrumental assessment. These patients, who are at heightened risk of pneumonia, can then be managed more appropriately and secondary complications can be avoided.

Proposed study

The aim of this study was to evaluate the clinical utility of CRT for reducing pneumonia and other functional indices in acute stroke patients using a facemask method ideal for the neurologically impaired patient and a tussive agent concentration based on normative data. Three hundred and eleven participants were randomly assigned to a control group or an experimental group across four urban hospitals. For patients in the experimental group, CRT was added to the clinical swallowing evaluation. The primary outcome was proportion of patients with pneumonia within three months post stroke (Chapter Eleven).

PART B: VALIDATION STUDIES

CHAPTER SEVEN

STUDY I. VALIDATING COUGH REFLEX TESTING AGAINST INSTRUMENTAL ASSESSMENT OF ASPIRATION [6] - VIDEOFLUOROSCOPY [7]

7.1 Hypotheses and Rationale

Silent aspiration is associated with increased prevalence of pneumonia and is poorly identified by traditional CSE. CRT provides information about airway sensitivity and therefore may act as a surrogate for silent aspiration and indicate those at most risk of not responding to airway irritation (Hypothesis 6.1).

7.2 Methodology

Eighty consecutive consenting patients (48 male, 32 female) referred for VFSS by their treating clinician as part of their standard inpatient or outpatient dysphagia management were recruited. The patients ranged in age from 22-100 years (mean 67 years, SD 18.75). Patients were excluded if they were tracheostomised or required oxygen support for respiratory and/ or spinal injuries. This study received appropriate regional ethics approval (Upper South B Regional Ethics Committee URB/10/06/019) and all participants

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[6] *Miles, A., Moore, S., McFarlane, M., Lee, F., Allen, J. & Huckabee. ML. (early online) Validating cough reflex testing against instrumental assessment of aspiration. Journal of Physiology and Behavior. DOI: http://dx.doi.org/10.1016/j.physbeh.2013.05.004*

[7] *This study, alongside Study II, was designed by a research team including the PhD Candidate. The data for this study was collected by Sara Moore as part of her Masters Degree. With Sara's consent, these data have been independently analysed with extended statistical procedures and reported in this thesis alongside Study II endoscopy data in view of its value to the discussion of CRT validation.*

gave informed consent independently or consent was gained by proxy. All patients completed a cough reflex threshold test and a VFSS. Independent researchers performed each test and were blinded to the result of the alternate test. Due to logistics of radiology booking schedules, CRT was performed within 30 minutes after completion of VFSS. All videofluoroscopic assessments were recorded and scored by two researchers from the video recordings.

7.2.1 Protocol.

Patients were seated upright in a chair. Citric acid solutions diluted in 0.9% sodium chloride were prepared by hospital pharmacies on a weekly basis. Incremental concentrations of 0.4mol/L, 0.6mol/L and 0.8mol/L were chosen based on established normative data which identified that 92.5% of healthy individuals produce a natural cough at 0.8mol/L (Monroe et al., 2010). Citric acid concentrations were administered for 15 seconds via facemask using a PulmoMate Compressor/Nebuliser (Model 4650I, DeVilbiss Healthcare LLC, Pennsylvania, US) with a predetermined free-flow output of 8 litres and a restricted flow output of 6.6 litres per minute. Patients were asked to breathe normally and cough "if they felt the need to cough". Initially a placebo dose of 0.9% NaCl was presented to accommodate the patient to the feel and noise of the nebuliser. Citric acid concentrations were administered incrementally from low to high in one-minute intervals. As recommended by the European Respiratory Society (ERS) Task Force, a placebo dose was interspersed between each change in citric acid dose to prevent tachyphylaxis and blunting of response to lower doses (Morice et al., 2007). Presence or absence of cough during the 15-second delivery period was documented. Cough response was considered positive if two or more consecutive coughs were triggered (C2 response threshold) (Morice et al., 2007). The test was repeated three times at each concentration with two out of three trials considered a positive result. If a

positive result was achieved, further thresholds were not tested. If the patient passed the cough test, a subjective judgement of cough strength was recorded (strong or weak). Patients were therefore given two scores: a threshold (0.4, 0.6, 0.8, 1.2, or fail) and a cough strength judgement (strong pass, weak pass or fail). Researchers received on-site training in the cough threshold test protocol, which included tasks to achieve consensus on cough interpretation (present/absent, strong/weak). The definition for weak cough provided to clinicians was "a cough that does not appear strong enough to clear aspiration and is substantially weaker than their own reflexive cough."

VFSS was conducted by hospital clinicians as per clinical protocol in the radiology suite (Philips, MultiDiagnost Eleva, Netherlands) and recorded at 30 frames/second onto videocassette recorder (Panasonic AG, 8700E, Japan) for frame-by-frame playback. Patients were administered a standard protocol of volumes and consistencies of barium contrast agents (Liquid Polibar, EZ paste, EZEM Canada Inc) (3 x 5ml apple sauce, 3 x sip of water, 3 x sip of mildly thickened juice (as a compensatory strategy if aspirated on thin), 3 x bites of banana, 3 x bites of barium on white bread, 3 x bites of barium on hard cracker and 20ml continuous drinking). The protocol was modified as required for patient safety. Images were obtained in antero-posterior and lateral planes. Airway protection was evaluated using the validated 8-point PAS (Rosenbek et al., 1996). The highest PAS score in the full study was recorded. As the primary symptom of interest was silent aspiration rather than dysphagia severity, if the patient aspirated, the study was also scored as i) no aspiration, ii) audible cough (aspirated and coughed) regardless of the effectiveness of the cough iii) silent aspiration (no cough response) with any single silent aspiration event scored as ‘silent aspiration’ even if audible aspiration was also noted. Aspiration was defined as material that touched the vocal cords or below.

7.2.2 Data analysis.

Statistical analyses were completed using SPSS version 20 (SPSS, Chicago, IL, USA). Cohen's kappa was used to assess rater agreement for PAS scores between the two researchers. Landis and Koch's classification was used for analysis (< 0 = no agreement, 0 – .20 = slight, .21 – .40 = fair, .41 – .60 = moderate, .61 – .80 = substantial, and .81 – 1.0 = almost perfect agreement) (Landis & Koch, 1977). The correlation between cough reflex test and instrumental assessment was analysed using Pearson's Chi-square test or Fisher's Exact Test (where expected counts were low and assumptions for Chi-square test were violated). Effect sizes were calculated using ORs [with 95% confidence intervals (C.I.s)]. Demographic and clinical factors (gender, age, cause of dysphagia) were chosen through bi-variable analysis against: i) CRT, ii) VFSS or iii) agreement between CRT and VFSS (agreed vs. did not agree regarding airway sensitivity). Firstly the full model with all significant confounding factors was fit, and a backward selection was used to select the main effect model. The significant two-way interactions (CRT and gender, CRT and cause of dysphagia) were then added in the main effect model one by one for the final model.

Sensitivity, specificity, positive predictive (PPV) and negative predictive (NPV) values (with 95% C.I.s) were calculated. Positive likelihood ratios (LR+), negative likelihood ratios (LR-), pre-test and post-test odds and probabilities were also calculated. A first analysis compared silent aspirators to all other cohort participants (including audible aspirators and non-aspirators) to represent the capacity of CRT for accurately identifying silent aspiration during a clinical examination. The second analyses compared silent aspirators to audible aspirators (excluding non-aspirators from the cohort) to assess the true validity of CRT for identifying silent aspirators. Finally, validity was presented graphically as a receiver operating characteristic curve (ROC curve) demonstrating the trade off between sensitivity and specificity at different thresholds. Overall accuracy at each threshold was evaluated using

AUC. This was considered a pilot study and no power calculation was made. A p value of < 0.05 was considered significant.

7.3 Results

7.3.1 Patient characteristics.

Eighty patients were recruited for the study; their primary aetiologies were stroke (18), head and neck (15), respiratory (12), progressive neurological disease (5), other neurological disease or injury (8) and other (22). Within the 'other' category, three patients were referred for dysphagia or oesophageal dysphagia with no other aetiology.

7.3.2 Test results.

During VFSS, 24/80 patients aspirated (30%), with 17/24 (70%) aspirating silently. The prevalence of silent aspiration was 21% (OR 0.28). Inter-rater agreement was high for PAS scores between two blinded raters (percentage agreement 96%, $\kappa = .95$). Seventy-five percent of patients passed CRT half of whom had a cough rated as weak by raters (Table 7.1).

7.3.3 Validation of CRT.

There was a significant association between CRT result (strong, weak or fail) and cough response to aspiration (no aspiration, aspiration with cough, aspiration without cough) (unadjusted $X^2 = 11.05$, $p = .003$, adjusted $X^2 = 18.69$, $p < .001$). Power was not sufficient to calculate the association between CRT result and PAS scores. The tabulated counts of CRT threshold results in comparison to cough response to aspiration and PAS scores are displayed in Table 7.2 and 7.3 respectively.

Table 7.1 CRT and VFSS results

		Number of patients
Cough Reflex Test result	*pass*	30/80 (37.5%)
	0.4	16
	0.6	9
	0.8	5
	1.2	0
	weak pass	30/80 (37.5%)
	0.4	10
	0.6	8
	0.8	6
	1.2	6
	fail	20/80 (25%)
VFSS result	*no aspiration*	56 (70%)
	aspirated and coughed	7 (9%)
	no cough to aspiration	17 (21%)

Table 7.2 Association between CRT result and cough response to aspiration

		Response to aspiration on VFSS		
		No aspiration	*Aspirated and coughed*	*No cough to aspiration*
CRT result	*strong pass*	**27**	2	1
	weak pass	20	4	6
	fail	9	1	**10**

Table 7.3 Association between CRT result and PAS score

		Highest Penetration Aspiration Score during VFSS							
		1	2	3	4	5	6	7	8
CRT result	*strong pass*	**14**	13	0	0	0	0	2	1
	weak pass	4	13	3	1	0	0	4	5
	fail	2	7	0	0	0	0	1	**10**

Although demographic and clinical variables did not significantly alter the final model between CRT and VFSS, CRT was significantly associated with cause of dysphagia, with 56% of stroke patients failing CRT compared with only 15% of respiratory patients (X^2 = 18.85, p = .011). Patients with a stroke had an OR of failing CRT of 16.7 (95% C.I. 2.27, 122.21). CRT was also significantly associated with gender with 35% of males failing CRT compared with only 9% of females and an OR of failing CRT if you were male of 8.5 (95% C.I. 2.04, 35.46) (X^2 = 10.96, p = .004). A significant association between lower cough threshold and female gender was also found with more females passing at 0.4mol/L (male: fail 35%, 1.2mol/L 8%, 0.8mol/L 13%, 0.6mol/L 21%, 0.4mol/L 23%; female: fail 9%, 1.2mol/L 6%, 0.8mol/L 16%, 0.6mol/L 22%, 0.4mol/L 47%, X^2 (1-tailed) = 8.86, p = .033). There was a two-way interaction between gender and agreement between CRT and VFSS (X^2 = 13.75, p = .022). Males had an OR of 6.2 (95% C.I. 1.30, 29.41) for having a disassociation between their CRT and VFSS result.

The proportion of audible aspirators on instrumental assessment who passed CRT was high (6/7, 86%) with only one audible aspirator failing CRT. The proportion of silent aspirators on instrumental assessment who failed a CRT (at 1.2mol/L) was 7/10, 59%. If a weak CRT result was considered a failed cough test (i.e., a weak response to citric acid), the proportion of silent aspirators who fail a CRT was higher (16/17, 94%) but this trade-off conversely reduced the agreement between audible aspirator and a passed cough test (2/7, 29%). Table 7.4 displays association test results and ORs for silent aspiration based on CRT threshold and classification of weak CRT result.

Further analysis of instrumental assessment compared to CRT demonstrated a dose dependent change in OR for silent aspiration. For aspirators, OR = 9 for silent aspiration with failed CRT at 1.2mol/L (at 0.8mol/L OR = 11; at 0.6mol/L OR = 6; at 0.4mol/L OR = 4). In the full cohort, patients who failed CRT at 1.2mol/L had an OR= 8 (at 0.8mol/L OR =

6; at 0.6mol/L OR = 4; at 0.4mol/L OR = 2). Wide confidence intervals mean these ORs should be interpreted with caution.

Sensitivity and specificity values for CRT were first calculated on data from the subgroup of patients who aspirated. For the aspirators only, sensitivity and specificity differed at different thresholds and was optimised at 0.6mol/L (71%, 71% respectively) (Table 7.5). AUC values were variable across thresholds and only 1.2mol/L reached significance: at 1.2mol/L AUC = .75 (95% C.I. .55, .96, p = .051); at 0.8mol/L AUC = .69 (95% C.I. .46, .92, p = .143); at 0.6mol/L AUC = .56 (95% C.I. .31, .81, p = .621) and at 0.4mol/L AUC = .63 (95% C.I. .38, .87, p = .333) (Figure 7.1). Likelihood ratios (with 95% C.I.s) and post-test probabilities across thresholds are found in Table 7.6. The LR+ for silently aspirating if a patient failed CRT (at 0.6mol/L) was 3.3 [with LR+ post-test odds rising to 7.9 (89% post-test probability) from pre-odds ratio of 2.4 (71% pre-test probability)]. The LR- for silently aspirating if a patient failed CRT (at 0.6mol/L) was 0.1 with a post-test odds dropping to 0.2 (16% post-test probability).

Table 7.4 Tests of association

		Pearson's Chi Squared Test		*p value*		*Odds Ratio (95% C.I.)*	
		Full cohort	*Aspirators only*	*Full cohort*	*Aspirators only*	*Full cohort*	*Aspirators only*
1.2	*strong weak/ fail*	9.21	2.34	.002	.127	13.65 (1.71, 292.64)	6.4 (0.33, 229.56)
	strong/ weak vs. fail	13.17	3.96	< .001	.047	7.57 (2.03, 29.44)	8.57 (0.69, 236.61)
0.8	*strong vs. weak/ fail*	9.21	2.33	.002	.127	13.65 (1.71, 292.64)	6.4 (0.33, 229.56)
	strong/ weak vs. fail	10.21	5.04	< .001	.025	5.87 (1.63, 21.90)	11.0 (0.87, 308.99)
0.6	*strong vs. weak/ fail*	6.47	11.36	.011	< .001	9.85 (1.23, 211.73)	40.0 (2.19,1739.47)
	strong/ weak vs. fail	5.14	3.61	.023	.058	3.65 (1.02, 13.72)	6.0 (0.65, 68.63)
0.4	*strong vs. weak/ fail*	2.69	2.33	.101	.127	5.00 (0.60, 109.37)	6.4 (0.33, 229.56)
	strong/ weak vs. fail	0.79	2.52	.374	.112	1.74 (0.45, 7.26)	4.33 (0.49, 44.45)

Table 7.5 Probability tests

		Sensitivity % (95% C.I.)		*Specificity % (95% C.I.)*		*Positive Predictive Value % (95% C.I.)*		*Negative Predictive Value % (95% C.I.)*	
		Full cohort	*Aspirators only*	*Full cohort*	*Aspirators only*	*Full cohort*	*Aspirators only*	*Full cohort*	*Aspirators only*
1.2	*strong (30) vs. weak/fail (50)*	94% (0.72,0.99)	94% (0.85, 0.99)	46% (0.40, 0.48)	29% (0.06, 0.42)	32% (0.24, 0.34)	76% (0.68, 0.81)	97% (0.84, 0.99)	67% (0.13, 0.98)
	strong/weak (N: 60) vs. fail (N:20)	59% (0.36, 0.78)	59% (0.43, 0.64)	84% (0.78,0.89)	86% (0.48, 0.99)	50% (0.31, 0.66)	91% (0.66, 0.99)	88% (0.82, 0.94)	46% (0.36, 0.53)
0.8	*strong (N: 30) vs. weak/fail (N: 50)*	94% (0.72, 0.99)	94% (0.85, 0.99)	46% (0.40,0.48)	28% (0.06, 0.42)	32% (0.24, 0.34)	76% (0.69, 0.81)	97% (0.84, 0.99)	67% (0.13, 0.98)
	strong/weak (N: 54) vs. fail (N: 26)	65% (0.41, 0.84)	65% (0.49, 0.70)	76% (0.70, 0.81)	86% (0.47, 0.99)	42% (0.27,0.55)	91% (0.69, 0.99)	89% (0.82, 0.95)	50% (0.28, 0.58)
0.6	*strong (N: 25) vs. weak/fail (N: 55)*	94% (0.72, 0.99)	94% (0.80, 0.99)	38% (0.32,0.40)	71% (0.36, 0.85)	29% (0.22,0.31)	89% (0.75, 0.94)	96% (0.81, 0.99)	83% (0.42, 0.99)

	strong/weak (N: 43) vs. fail (N: 37)	71% (0.47, 0.88)	71% (0.55, 0.80)	60% (0.54, 0.65)	71% (0.34, 0.95)	32% (0.21, 0.41)	86% (0.67, 0.97)	88% (0.79, 0.95)	50% (0.24, 0.66)
0.4	*strong (N: 16) vs. weak/fail (N: 64)*	94% (0.73, 0.99)	94% (0.85, 0.99)	24% (0.18, 0.25)	29% (0.06, 0.42)	25% (0.19, 0.27)	76% (0.69, 0.81)	94% (0.71, 0.99)	67% (0.13, 0.98)
	strong/weak (N: 26) vs. fail (N: 54)	77% (0.53, 0.92)	77% (0.62, 0.88)	35% (0.29, 0.39)	57% (0.23, 0.86)	24% (0.17, 0.29)	81% (0.66, 0.94)	85% (0.69, 0.95)	50% (0.20, 0.75)

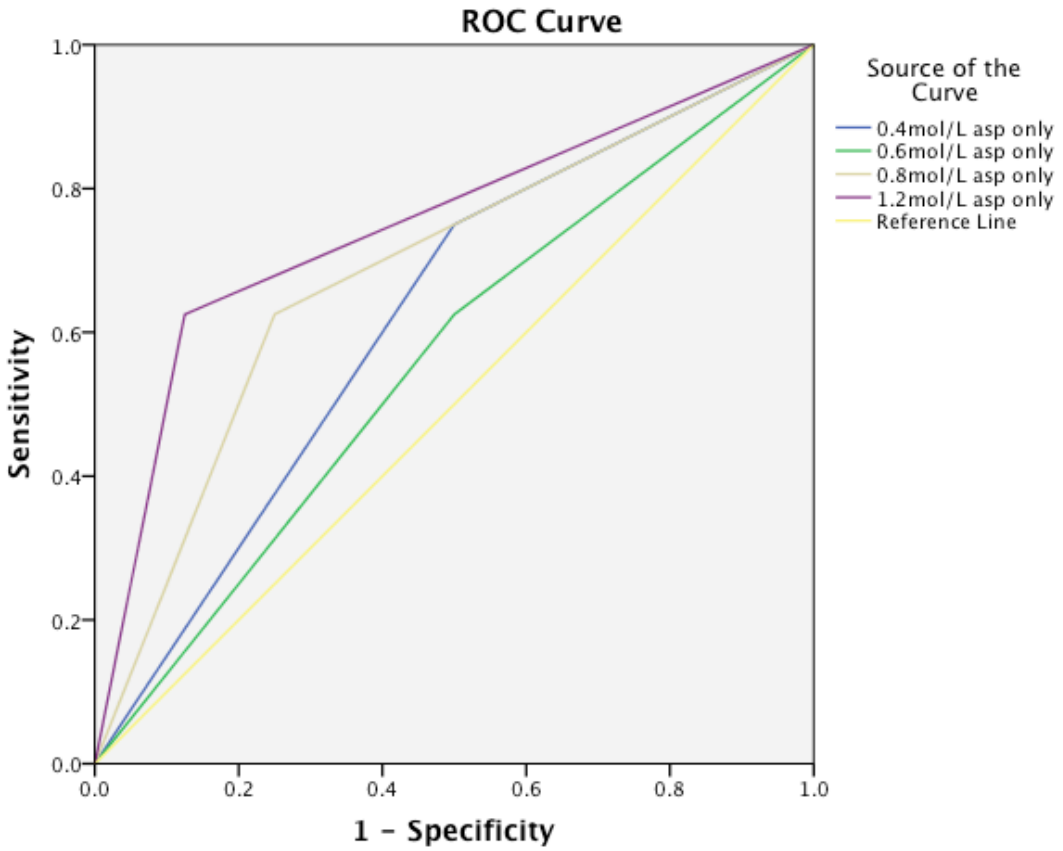


Figure 7.1 ROC curve demonstrating the trade off for aspirators between sensitivity and specificity at different thresholds

The validity of CRT was weaker when non-aspirators were added to the analysis compared with the aspirators-only analysis. The trade-off between sensitivity and specificity at different thresholds is still evident and reported in Table 7.5 with 0.4mol/L reaching the highest sensitivity (77%) and 1.2mol/L the highest specificity (84%). AUC values were again variable and only 0.8mol/L and 1.2mol/L reached significance: at 1.2mol/L AUC = .73 (95% C.I. .58, .89, p = .004); at 0.8mol/L AUC = .69 (95% C.I. .54, .84, p = .021); at 0.6mol/L AUC = .64 (95% C.I. .49, .79, p = .083) and at 0.4mol/L AUC = .55 (95% C.I. .39, .70, p = .564) (Figure 7.2).

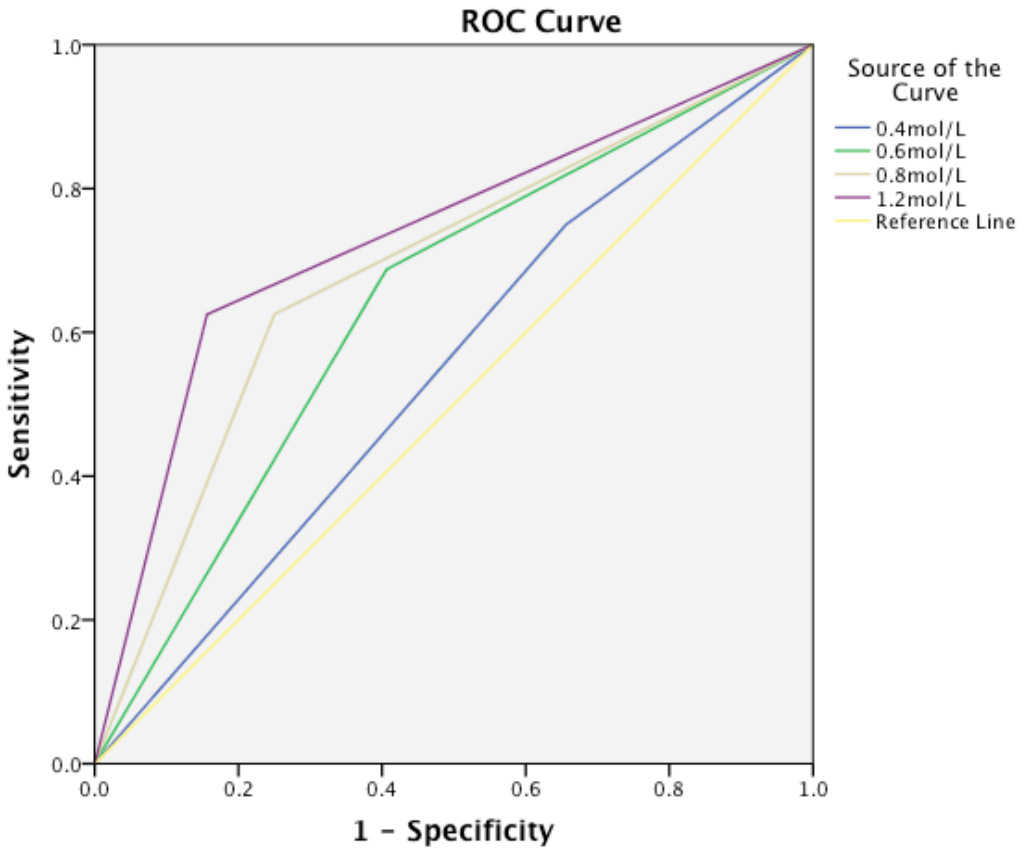


Figure 7.2 ROC curve demonstrating the trade off between sensitivity and specificity at different thresholds

Likelihood ratios (with 95% CIs) and post-test probabilities are displayed in Table 7.6. The highest LR+ for silently aspirating if a patient failed CRT (at 0.8mol/L) was 2.7 [with post-test odds rising to 0.8 (post-test probability 43%) from pre-odds ratio of 0.3 (pre-test probability 21%)]. The LR- for silently aspirating if a patient failed CRT (at 0.6mol/L) was 0.2 with a post-test odds dropping to 0.2 (13% post-test probability)

Table 7.6 Likelihood ratios (aspirators only)

		Prevalence of silent aspiration (pre-odds ratio)	*Likelihood Ratio of positive test results (LR+)*		*Likelihood Ratio of negative test results (LR-)*	
			L + (95% C.I.)	*Post-test probability (post test odds)*	*LR – (95% C.I.)*	*Post-test probability (post test odds)*
1.2	*strong vs. weak/ fail*	71%	1.32 (0.90, 1.72)	76% (3.17)	0.21 (0.01, 2.72)	33% (0.49)
	strong/ weak vs. fail	71% (2.4)	4.12 (0.82, 84.89)	91% (9.89)	0.48 (0.36, 1.20)	54% (1.15)
0.8	*strong vs. weak/ fail*	71% (2.4)	1.32 (0.90, 1.72)	76% (3.17)	0.21 (0.01, 2.72)	33% (0.49)
	strong/ weak vs. fail	71% (2.4)	4.53 (0.93, 92.55)	92% (10.87)	0.41 (0.30, 1.08)	50% (0.99)
0.6	*strong vs. weak/ fail*	71% (2.4)	3.29 (1.24, 6.61)	89% (7.90)	0.08 (0.00, 0.57)	16% (0.20)
	strong/ weak vs. fail	71% (2.4)	2.47 (0.84, 14.48)	86% (5.93)	0.41 (0.21, 1.30)	50% (0.99)
0.4	*strong vs. weak/ fail*	71% (2.4)	1.32 (0.90, 1.72)	76% (3.16)	0.21 (0.01, 2.72)	33% (0.49)
	strong/ weak vs. fail	71% (2.4)	1.78 (0.81, 6.13)	81% (4.28)	0.41 (0.14, 1.65)	50% (0.99)

Table 7.7 Likelihood ratios (full cohort analysis)

		Prevalence of silent aspiration (pre-odds ratio)	*Likelihood Ratio of positive test results (LR+)*		*Likelihood Ratio of negative test results (LR-)*	
			L + (95% C.I.)	*Post-test probability (post test odds)*	*LR – (95% C.I.)*	*Post-test probability (post test odds)*
1.2	*strong vs. weak/ fail*	21% (0.28)	1.74 (1.20, 1.90)	33% (0.48)	0.13 (0.01, 0.70)	3% (0.04)
	strong/ weak vs. fail	21% (0.28)	3.71 (1.65, 7.27)	51% (1.02)	0.49 (0.25, 0.82)	12% (0.14)
0.8	*strong vs. weak/ fail*	21% (0.28)	1.74 (1.20, 190)	33% (0.48)	0.13 (0.01, 0.70)	3% (0.04)
	strong/ weak vs. fail	21% (0.28)	2.72 (1.37, 4.45)	43% (0.75)	0.46 (0.20, 0.84)	11% (0.13)
0.6	*strong vs. weak/ fail*	21% (0.28)	1.52 (1.06, 1.65)	30% (0.42)	0.15 (0.01, 0.87)	13% (0.15)
	strong/ weak vs. fail	21% (0.28)	1.78 (1.01, 2.52)	33% (0.49)	0.49 (0.18, 0.99)	12% (0.14)
0.4	*strong vs. weak/ fail*	21% (0.28)	1.24 (0.89, 1.34)	25% (0.34)	0.25 (0.01, 1.49)	6% (0.07)
	strong/ weak vs. fail	21% (0.28)	1.18 (0.74, 1.51)	24% (0.32)	0.67 (0.21, 1.65)	16% (0.19)

CHAPTER EIGHT

STUDY II. VALIDATING COUGH REFLEX TESTING AGAINST INSTRUMENTAL ASSESSMENT OF ASPIRATION [8] - ENDOSCOPY

8.1 Hypotheses and Rationale

See 7.1 (6.1. Study I and II Hypotheses and rationale).

8.2 Methodology

The cohort consisted of 101 consecutive consenting inpatients (51 male, 50 female) ranging in age from 25-96 (mean 78 years, SD 12.6) referred to speech-language therapy for initial swallowing assessment. Patients were excluded if they were deemed by a researcher to be too drowsy or medically unstable for either of the investigations, were tracheostomised or where evaluation was contraindicated (e.g., nasal anatomical abnormalities, history of severe epistaxis, base of skull fractures).

8.2.1 Study design.

This study received appropriate regional ethics approval (Northern Y Ethics Committee NTY/11/04/038). All participants gave informed consent independently or consent was given by proxy. All patients completed CRT and FEES with two researchers blinded to the result of the other assessment. The order of CRT and FEES was alternated to

[8] *Miles, A., Moore, S., McFarlane, M., Lee, F., Allen, J. & Huckabee. ML. (early online) Validating cough reflex testing against instrumental assessment of aspiration. Physiology and Behavior. DOI: http://dx.doi.org/10.1016/j.physbeh.2013.05.004*

avoid order bias and the tests were separated by one hour (range 45-90 minutes). All FEES assessments were recorded, stored on the hard drive of the DVD player and scored from the video recording by two researchers. In order to assess agreement of CRT scoring, all CRTs were also video-recorded using a Mino HD flip video camera (CISCO, Irvine, CA), stored on a laptop for playback and scored by two researchers.

8.2.2 Protocol.

CRT was administered as per the protocol described in Study I, Section 7.2. Citric acid solutions diluted in 0.9% sodium chloride for this study included 0.4mol/L, 0.6mol/L and 0.8mol/L. The endoscopic swallowing assessment was performed by one of the researchers at the patient's bedside. A 3.2 mm diameter flexible video rhino-laryngoscope (Olympus, ENF V2) was passed through the nose and positioned in the pharynx. Using an integrated light source and video processor (Olympus, OTVS.I), the pharynx and larynx were viewed on an LCD Monitor (Olympus OEV203). The patient was given food and fluids (3 x 5ml apple sauce, 3 x sip of milk, 3 x bites of cheese sandwich, 20ml continuous drinking of milk from a straw). If the patient aspirated on sips of milk, 3 x sips of mildly thickened fluids were given (Thickened Creamy Based Mildly Thick Nectar Level 1, Flavor Creations Australia) as a compensatory strategy. If the patient demonstrated significant aspiration during the study, the protocol was modified or truncated for safety reasons. To improve visualisation during the procedure, trials were mixed with blue food colouring (Hansells Blue Colouring Old Fashioned Foods Ltd NZ). Aspiration scoring is described in Study I, Section 7.2. Subjective judgement of strength (strong vs. weak) and speed (prompt vs. latent) of response to aspiration was documented. Again, researchers developed consensus on cough judgements of both strong/weak cough and prompt/latent cough prior to recruitment. The definition for weak cough provided to clinicians was "a cough that does not appear strong

enough to clear aspiration." Finally, subjective judgement of trace aspiration was documented, in line with previous research, as trace amounts of aspiration are easily visualised on endoscopic view but may not be clinically relevant (Wakasugi et al., 2008).

8.2.3 Data analysis.

Statistical analyses were completed using SPSS version 20 (SPSS, Chicago, IL, USA) and the analysis approach has been described previously. For details see Study I, Section 7.2. With a presumed overall agreement probability of 50% or more, a sample size of 100 patients was calculated with a relative error of 20% (Gwet, 2010).

8.3 Results

One hundred and one patients were recruited for the study (51 male, 50 female) with an average age of 77.96 years (range 25-96 years, SD 12.6). Most patients identified themselves as of New Zealand European (NZE) ethnicity (88), with 3 New Zealand Maori (NZM), 6 Asian, 1 Tongan, and 3 other. Their primary aetiologies were: stroke 50, progressive neurological disease 14, other neurological 8, head and neck 4, respiratory 18, other 7. Twenty-five percent of patients had respiratory comorbidities (COPD 15, smoker 1, asthma 6, bronchiolectisis 1, emphysema 2). Twenty-five percent of patients were taking ACE inhibitors. Seventy-one percent were new onset dysphagia while 29% had dysphagia prior to admission.

Sixty-two percent of patients aspirated (63/101); 57% aspirated silently (36/63). The most frequently aspirated materials were continuous fluid drinking (26/59, 44% of those trialled at this level), sips of thin fluids (38/96, 40% of those trialled) and thickened fluids (13/32, 41% of those trialled) (Table 8.1). Eight aspiration events were classified as trace; none of these events led to a cough. Eight patients overtly aspirated on one trial but silently

aspirated on another trial. Interestingly, four patients overtly aspirated on thin fluids but silently aspirated on thick fluids. All four of these patients had a weak cough reflex test result (Table 8.2).

Table 8.1 Raw data for rates of aspiration and silent aspiration

		Number of patients (% of those tested)
Aspirated on… (PAS score 4-8)	*sips of thin fluids*	38/96 (40%)
	continuous thin fluids	26/59 (44%)
	thickened fluids	13/32 (41%)
	puree	9/101 (9%)
	solids	2/58 (3%)
Silently aspirated on… (PAS score 5 or 8)	*sips of thin fluids*	17/96 (18%)
	continuous thin fluids	12/59 (20%)
	thickened fluids	9/32 (28%)
	puree	4/101 (4%)
	solids	1/58 (2%)

Table 8.2 Mixed aspirators

Overt aspiration	*Silent aspiration*	*CRT result*
thin & thick	solids	Fail
puree	thin	Fail
continuous thin	thin and thick	0.4 strong
thin	thin	0.4 strong
thin and solids	thick	0.4 weak
thin	thick	0.6 weak
thin	thick	0.6 weak
thin	thick	0.4 weak

8.3.1 Cough reflex test results.

Seventy-eight patients passed the CRT (strong 53, weak 24) and 23 failed the CRT (Table 8.3). There was no significant association between CRT result and gender (male: fail 23%, weak 30%, strong 47%; female: fail 22%, weak 24%, strong 54%; X^2 (2) = 0.54, p = .762). Again, there was a significant association between lower cough thresholds and female gender (male: fail 23%, 0.8mol/L 10%, 0.6mol/L 18%, 0.4mol/L 49%; female: fail 22%, 0.8mol/L 0%, 0.6mol/L 12%, 0.4mol/L 66%; X^2 (1-tailed) = 6.74, p = .042).

Forty-three patients completed their FEES prior to their CRT (15 did not aspirate, 12 aspirated and coughed and 16 silently aspirated) while 58 patients completed the CRT first (24 did not aspirate, 15 aspirated and coughed and 19 silently aspirated). There was no significant difference in aspiration response depending on the order of tests (U = 1160, z = 0.64, p = .529, r = .06).

Table 8.3 CRT results

CRT result	*pass*		53/101 (52%)
		0.4	42
		0.6	10
		0.8	1
	weak pass		24/101 (24%)
		0.4	15
		0.6	6
		0.8	4
	fail		23/101 (23%)

More detailed analysis of patients with active pneumonia found 33/101 patients had pneumonia on the day of assessment. In those with pneumonia, CRT results were fail 30.3%

(10), weak 27.3% (9) and strong 42.4% (14) while in those who did not have pneumonia, CRT rates were fail 19.1% (13), weak 26.5% (18) and strong 54.4% (37). There was no significant association between cough result (strong pass, weak pass, fail) and pneumonia diagnosis ($X^2 = 1.86$, $p = .416$). There was also no significant association between cough threshold (0.4mol/L, 0.6mol/L, 0.8mol/L, fail) and pneumonia diagnosis ($X^2 = 1.89$, $p = .631$). No significant association was found between silent aspiration and pneumonia, with silent aspiration rates of 42.4% in the pneumonia group vs. 35.3% in the no pneumonia group ($X^2 = 0.48$, $p = .488$).

8.3.2 Inter-rater reliability.

Inter-rater agreement was high between the two raters across nine ratings (range of percentage agreement 96-100%, range of κ values .91-1.00) (Table 8.4).

Table 8.4 Inter-rater reliability between judges' ratings

Rating	*Percentage Agreement*	*Kappa*
cough reflex threshold (0.4, 0.6, 0.8, FAIL)	96%	.98
cough presence/ absence within CRT	99%	.97
cough strength (normal/ weak) within CRT	96%	.94
PAS scoring (thin) within FEES	98%	.96
PAS scoring (puree) within FEES	97%	.91
cough presence/ absence within FEES	98%	.97
cough strength (normal/ weak) within FEES	100%	1.00
cough latency (prompt, latent) within FEES	97%	.94
trace aspiration vs. aspiration	100%	1.00

8.3.3 Validation of the cough reflex test.

Tables 8.5 and 8.6 contain the tabulated counts of CRT threshold results in comparison to cough response to aspiration and PAS scores respectively. There was a significant association between CRT result (strong, weak, fail) and cough response to aspiration (no aspiration, aspiration with cough, aspiration without cough) (unadjusted X^2 = 34.08, $p < .001$, adjusted $X^2 = 26.42$, $p < .001$) (Table 8.7).

Table 8.5 Association between cough reflex threshold and cough response to aspiration

		Response to Aspiration on FEES			
		Did not aspirate	*Aspirated and coughed*	*Silent aspiration*	
				Aspiration	*Trace aspiration*
CRT Result	*0.4 strong*	**20**	**16**	2	4
	0.4 weak	4	6	2	3
	0.6 strong	4	2	2	2
	0.6 weak	2	1	3	0
	0.8 strong	1	0	0	0
	0.8 weak	1	1	2	0
	fail	6	1	**16**	0

Table 8.6 Association between CRT result and PAS score

		Highest Penetration Aspiration Score during FEES							
		1	2	3	4	5	6	7	8
CRT Result	*strong pass*	**22**	1	1	**14**	2	4	2	5
	weak pass	3	1	1	8	7	1	0	5
	fail	4	2	0	1	**5**	2	3	**6**

Table 8.7 Association between silent aspiration and CRT result at 0.4mol/L

		Wald statistic	*p value*	*Odds Ratio*	*95% C.I.*
Silent aspiration on FEES	*pass CRT*	10.18	< .001	0.2	0.05, 0.49
	weak CRT	10.18	< .001	6.3	2.04, 19.68
	fail CRT	4.74	.030	6.3	1.20, 33.38

The proportion of overt aspirators on instrumental assessment who passed CRT (at 0.8mol/L) was high (26/27, 96%) with only one overt aspirator failing CRT. The proportion of silent aspirators who failed CRT (at 0.8mol/L) was lower (16/36, 44%). Table 8.8 reports association test results and ORs for silent aspiration for the full cohort and for the aspirators only. Aspirators who failed CRT at 0.8mol/L had an OR of 38 for silently aspirating, an OR of 25 if failing the CRT at 0.6mol/L or 0.4mol/L (trace aspirators removed). Confidence intervals were wide and these ORs should be interpreted with caution. In the full cohort, patients who failed CRT at 0.8mol/L had an OR of 12 for silently aspirating, an OR of 11 for failing the CRT at 0.6mol/L and 14 for failing the CRT at 0.4mol/L (trace aspirators removed).

Table 8.8 Tests of association (aspirators only)

		Chi Squared Test		*p value*		*Odds Ratio (95% C.I.)*	
		Full cohort	*Aspirators only*	*Full cohort*	*Aspirators only*	*Full cohort*	*Aspirators only*
0.8	*strong (N:53) vs. weak/fail (N:48)*	13.68	9.45	< .001	.002	5.08 (1.92, 13.76)	5.20 (1.56, 17.98)
	strong/weak (N:78) vs. fail (N:23)	14.94	15.30	< .001	< .001	6.63 (2.16, 21.08)	20.80 (2.49, 456.32)
	with trace aspirators removed, strong (N:47) vs. weak/fail (N:45)	20.12	15.03	< .001	< .001	11.24 (3.13, 44.19)	11.50 (2.62, 55.46)
	with trace aspirators removed, strong/weak (N: 69) vs. fail (N:23)	23.92	19.32	< .001	< .001	12.05 (3.58,42.53)	37.82 (4.23,863.12)
0.6	*strong (N:52) vs. weak/fail (N:49)*	12.59	15.03	< .001	< .001	4.75 (1.80,12.80)	11.50 (2.62,55.46)
	strong/weak (N:73) vs. fail (N:28)	13.86	12.92	< .001	< .001	5.50 (1.96,15.75)	12.50 (2.31,89.41)
	with trace aspirators removed, strong (N: 46) vs. weak/fail (N: 46)	18.92	9.45	< .001	.002	10.50 (2.93,41.15)	5.20 (1.56,17.98)

	with trace aspirators removed, strong/weak (N:64) vs. fail (N: 28)	23.70	20.33	< .001	< .001	11.00 (3.46, 36.389)	25.00 (4.18,195.36)
	strong (N:42) vs. weak/fail (N:59)	14.30	12.32	< .001	< .001	6.21 (2.09, 19.33)	7.27 (1.99,27.99)
0.4	*strong/weak (N:57) vs. fail (N:34)*	15.24	16.04	< .001	< .001	5.50 (2.08, 14.84)	10.00 (2.64,40.54)
	with trace aspirators removed, strong (N:38) vs. weak/fail (N: 54)	18.11	16.33	< .001	< .001	15.52 (3.15, 103.58)	18.18 (3.11,138.72)
	with trace aspirators removed, strong/weak (50) vs. fail (42)	24.07	24.03	< .001	< .001	13.92 (3.83, 55.44)	25.3 (5.05,146.49)

CRT result (at 0.4mol/L) was also significantly associated with age, with greater mean age for weak CRT (85 years, SD 6.6) than failed CRT (77.1 years, SD 13.3) and strong CRT (76.3 years, SD 13.0) (X^2 = 22.12, p = .005). Although demographic and clinical variables did not alter the final model between CRT and FEES, there were a number of three-way interactions with adjusted odds ratios for weak and failed CRT results (Table 8.9).

Table 8.9 Multiple logistic regression for the association between CRT result and response to aspiration adjusted demographic and clinical factors

		Confirmed silent aspiration on FEES			
		Wald statistic	*p value*	*Odds Ratio*	*95% C.I.*
Over 65 years old	*weak CRT*	6.14	.013	10.8	1.64, 70.93
	fail CRT	11.71	< .001	8.6	2.51, 29.72
Neurological cause of dysphagia	*fail CRT*	4.07	.044	10.6	0.65, 154.40
Respiratory comorbidities	*fail CRT*	3.93	.047	15.0	1.03, 218.30

8.3.4 Cough strength and latency.

Subjective cough strength judgement on CRT (strong, weak or no cough) was significantly associated with subjective cough strength judgement in response to aspiration on FEES (X^2 = 15.25, p = .003). Subjective cough strength judgement on CRT (strong, weak or no cough) was also significantly associated with subjective judgement of speed of cough response to aspiration on FEES (prompt response, subjectively latent response, no response) (X^2 = 16.70, p < .001) (Table 8.10 and 8.11).

Table 8.10 Association between CRT result and subjective cough strength in patients who aspirated

		Subjective strength of response to aspiration on FEES		
		Strong response to aspiration	*Weak response to aspiration*	*No response to aspiration*
CRT Result	*strong pass*	16	3	8
	weak pass	12	3	12
	fail	1	1	15

Table 8.11 Association between CRT result and subjective cough latency in patients who aspirated

		Subjective speed of response to aspiration on FEES		
		Prompt response to aspiration	*Latent response to aspiration*	*No response to aspiration*
CRT Result	*strong pass*	18	2	7
	weak pass	7	5	9
	fail	2	1	14

8.3.5 Sensitivity/ specificity

Table 8.12 reports sensitivity, specificity, positive predictive values and negative predictive values across thresholds. Sensitivity and specificity values for CRT were first calculated on data from the subgroup of patients who aspirated. For the subgroup who aspirated, the trade-off between sensitivity and specificity was optimised at 0.4mol/L (69%, 71% respectively). Likelihood ratios (with 95% C.I.s) and post-test probabilities are found in Table 8.8. The likelihood ratio of a failed CRT if an aspirating patient silently aspirated was optimised at 0.4mol/L with a LR+ of 3.6 (with post odds ratio rising to 4.7 (82%

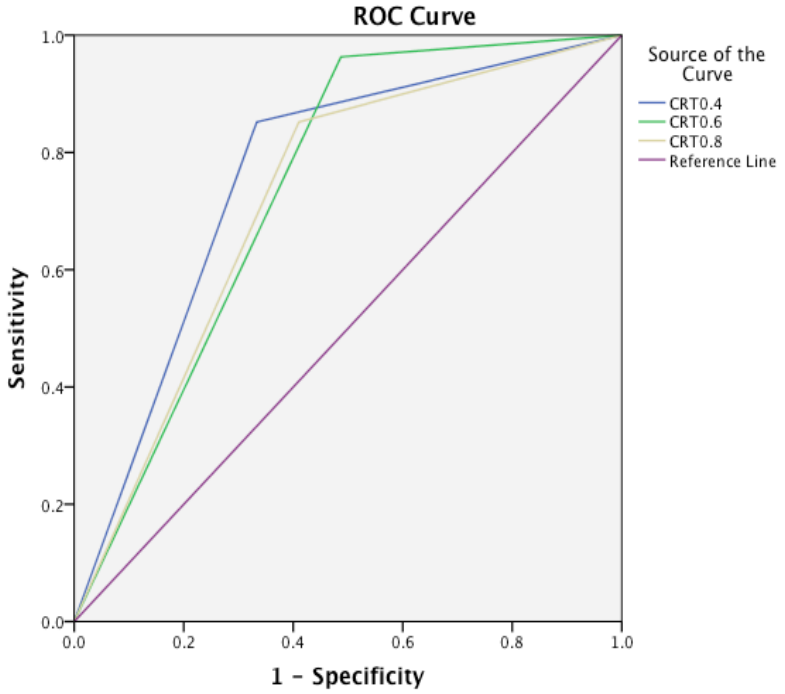
prevalence) from pre-odds ratio of 0.4 (33% prevalence). The LR- of a failed CRT if an aspirating patient silently aspirated was 0.38 with a post-test probability of 33% (post odds ratio 0.49).

The trade-off between sensitivity and specificity at different thresholds is demonstrated in Figure 8.1a with 0.4mol/L reaching the highest sensitivity (69%) and 0.8mol/L the highest specificity (89%). At 0.4mol/L AUC = .76 (95% C.I. .64, .88, $p < .001$), at 0.6mol/L AUC = .74 (95% C.I. .62, .86, $p < .001$), and at 0.8mol/L AUC = .72 (95% C.I. .60, .85, $p < .001$)].

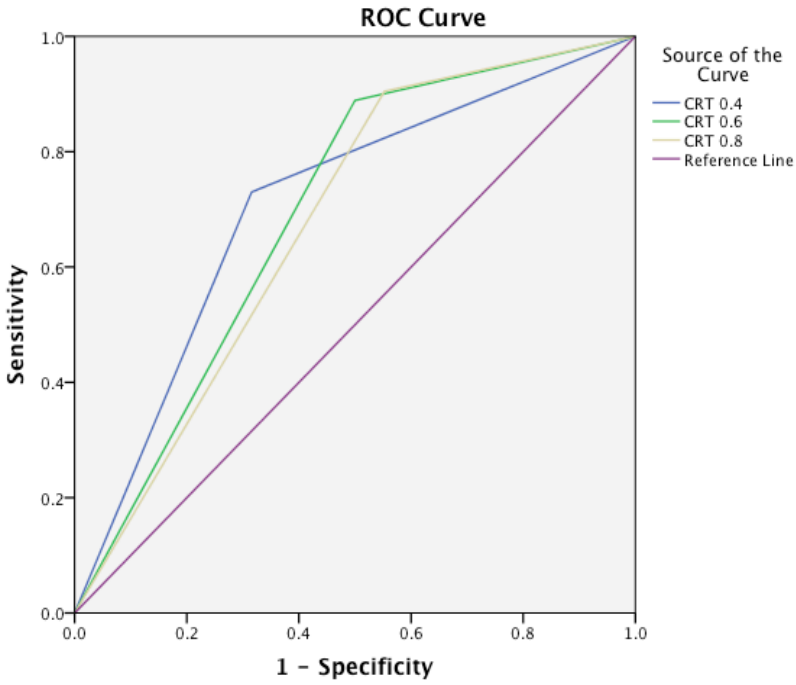
Table 8.12 Probability tests

		Sensitivity % (95% C.I.)		*Specificity % (95% C.I.)*		*Positive Predictive Value % (95% C.I.)*		*Negative Predictive Value % (95% C.I.)*	
		Full cohort	*Aspirators only*	*Full cohort*	*Aspirators only*	*Full cohort*	*Aspirators only*	*Full cohort*	*Aspirators only*
0.8	*strong (N:53) vs. weak/ fail (N:48)*	72% (0.58,0.84)	72% (0.60, 0.82)	66% (0.58,0.73)	67% (0.51, 0.80)	54% (0.43, 0.63)	74% (0.62, 0.84)	81% (0.71, 0.89)	64% (0.49, 0.77)
	strong/ weak (N:78) vs. fail (N:23)	44% (0.32, 0.54)	44% (0.34, 0.47)	89% (0.82, 0.95)	96% (0.83, 0.99)	70% (0.50, 0.85)	94% (0.73, 0.99)	74% (0.69, 0.79)	57% (0.49, 0.59)
	with trace aspirators removed, with strong (N:47) vs. weak/ fail (N:45)	85% (0.68, 0.95)	85% (0.71, 0.95)	66% (0.59, 0.70)	67% (0.52, 0.76)	51% (0.41, 0.57)	71% (0.596, 0.798)	91% (0.82, 0.97)	82% (0.64, 0.93)
	with trace aspirators removed, with strong/ weak (N: 69) vs. fail (N:23)	59% (0.43, 0.72)	59% (0.46, 0.63)	89% (0.83, 0.94)	96% (0.83, 0.99)	70% (0.51, 0.84)	94% (0.73, 0.99)	84% (0.78, 0.89)	70% (0.61, 0.73)
0.6	*strong (N:52) vs. weak/ fail (N:49)*	72% (0.58, 0.84)	72% (0.60, 0.82)	65% (0.57, 0.71)	66% (0.51, 0.80	53% (0.43, 0.62)	74% (0.62, 0.84)	81% (0.71, 0.89)	64% (0.49, 0.77)

	strong/ weak (N:73) vs. fail (N:28)	50% (0.37, 0.61)	50% (0.39, 0.55)	85% (0.77, 0.91)	93% (0.78, 0.99)	64% (0.47, 0.79)	90% (0.71, 0.98)	75% (0.69, 0.81)	58% (0.49, 0.62)
	with trace aspirators removed, with strong (N: 46) vs. weak/ fail (N: 46)	85% (0.68, 0.95)	85% (0.71, 0.95)	65% (0.58, 0.69)	66% (0.52, 0.76)	50% (0.40, 0.56)	72% (0.60, 0.80)	91% (0.81, 0.97)	82% (0.64, 0.93)
	with trace aspirators removed, with strong/ weak (N:64) vs. fail (N: 28)	67% (0.50, 0.80)	66% (0.53, 0.73)	85% (0.78, 0.90)	93% (0.79, 0.99)	64% (0.48, 0.77)	90% (0.71, 0.98)	86% (0.79, 0.92)	74% (0.63, 0.78)
0.4	*strong (N:42) vs. weak/ fail (N:59)*	83% (0.70, 0.93)	83% (0.72, 0.92)	55% (0.48, 0.61)	59% (0.44, 0.71)	51% (0.42, 0.57)	76% (0.63, 0.81)	86% (0.74, 0.94)	73% (0.54, 0.87)
	strong/ weak (N:57) vs. fail (N:34)	69% (0.55, 0.81)	69% (0.58, 0.78)	71% (0.63, 0.77)	81% (0.66, 0.92)	57% (0.45, 0.67)	83% (0.66, 0.93)	81% (0.72, 0.88)	67% (0.54, 0.75)
	with trace aspirators removed, with strong (N:38) vs. weak/ fail (N: 54)	93% (0.77, 0.99)	92% (0.79, 0.99)	55% (0.49, 0.58)	59% (0.46, 0.65)	46% (0.38, 0.49)	69% (0.59, 0.74)	95% (0.84, 0.99)	89% (0.68, 0.98)
	with trace aspirators removed, with strong/ weak (N:50) vs. fail (N:42)	85% (0.69, 0.95)	85% (0.71, 0.94)	71% (0.64, 0.75)	81 (0.67, 0.90)	55% (0.44, 0.61)	74% (0.62, 0.84)	92% (0.83, 0.97)	85% (0.70, 0.94)



a)



b)

Figure 8.1 ROC curve plot demonstrating the trade-off between sensitivity and specificity at 0.4mol/L, 0.6mol/L and 0.8mol/L a) aspirators only b) full cohort

Table 8.13 Likelihood Ratios (aspirators only)

		Prevalence of silent aspiration (pre-odds ratio)	*Likelihood Ratio of positive test results (LR+)*		*Likelihood Ratio of negative test results (LR-)*	
			LR+ (95% C.I.)	*Post-test probability (post test odds)*	*LR- (95% C.I.)*	*Post-test probability (post test odds)*
0.8	*pass vs. fail*	57% (1.3)	11 (1.98, 241.97)	93% (14.3)	0.58 (0.53, 0.79)	43% (0.75)
	with trace aspirators removed	50% (1)	16 (2.74, 321.98)	94% (14.75)	0.43 (0.37, 0.65)	30% (0.43)
0.6	*pass vs. fail*	57% (1.3)	6.8 (1.80, 41.17)	90% (8.77)	0.54 (0.46, 0.78)	41% (0.70)
	with trace aspirators removed	50% (1)	9.43 (2.50, 54.01)	90% (9.43)	0.37 (0.28, 0.60)	27% (0.37)
0.4	*pass vs. fail*	57% (1.3)	3.6 (1.699.91)	82% (4.68)	0.38 (0.24, 0.64)	33% (0.49)
	with trace aspirators removed	50% (1)	4.47 (2.179.71)	82% (4.47)	0.19 (0.07, 0.43)	16% (0.19)

8.3.6 Weak classification.

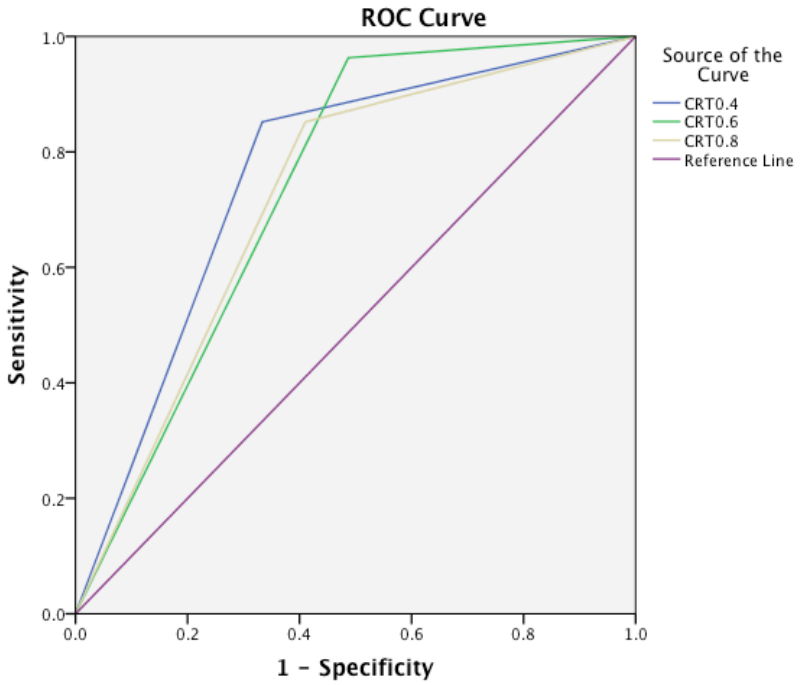
The trade-off between sensitivity and specificity when weak cough is classified as a fail rather than a pass is demonstrated in Figure 8.2 where classifying weak cough as a fail leads to a high sensitivity but a significant increase in false positives (at 0.4mol/L). The false positive rate when weak is classified as fail is 0.45; if weak is classified as a pass it is 0.29 (Table 8.12 for sensitivity and specificity values).

8.3.7 Trace aspirators.

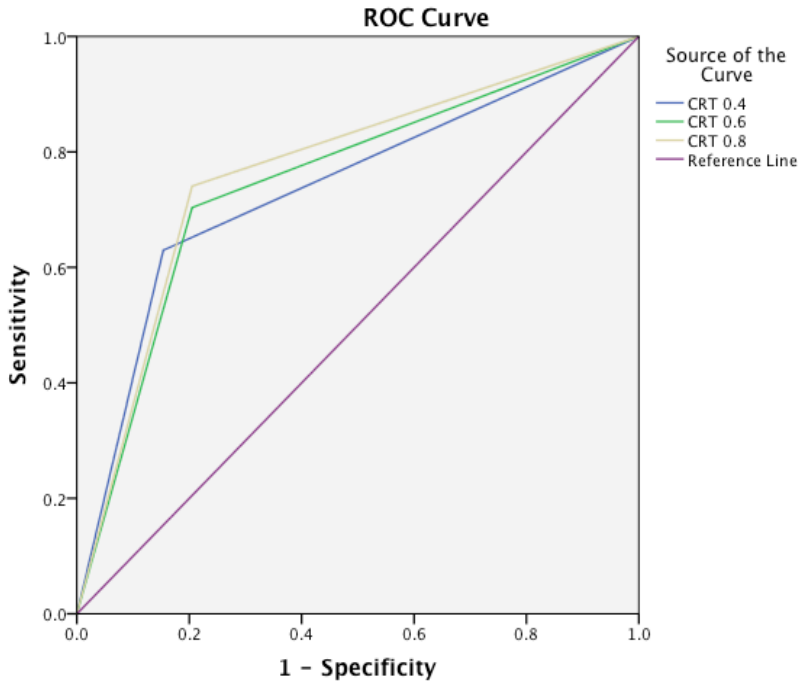
When trace silent aspirators were removed from analysis, the proportion of silent aspirators who fail CRT rises (16/27, 59%). Table 8.12 shows this increase in sensitivity with the highest sensitivity at 0.4mol/L (85%) and the highest specificity remaining at 0.6mol/L (93%). Likelihood ratios (with 95% C.I.s) and post-test probabilities are found in Table 8.13. The LR+ of silently aspirating if a patient failed CRT was greatest at 0.4mol/L with trace aspirators removed; LR+ was 4.5 with LR+ post-test odds rising to 4.5 (82% post-test probability) from pre-odds ratio of 1 (50% pre-test probability). The LR- post-test odds dropped to 0.2 with a post-test probability of 16%.

The diagnostic strength of CRT was weaker when non-aspirators were added to the analysis. The trade-offs between sensitivity and specificity at different thresholds are displayed in Table 8.12 and is again optimised at 0.4mol/L (69%, 71% respectively). The increase in sensitivity when trace aspirators are removed from analysis (85%) is apparent from reviewing the data. Likelihood ratios (with 95% C.I.s) and post-test probabilities are found on Table 8.14. The LR+ of silently aspirating if a patient failed CRT was greatest at 0.4mol/L with trace aspirators removed). The LR+ was 2.9 [with post-test odds rising to 2.3 (post-test probability 55%) from pre-odds ratio of 0.4 (pre-test probability 29%)]. The LR- was 0.2 (with a post-test odds of 0.09, post-test probability 8%).

Sensitivity and specificity of CRT at differing thresholds (0.4mol/L, 0.6mol/L, 0.8mol/L) is demonstrated in ROC curves with AUCs of .74 (95% C.I. .64, .84, $p < .001$), .77 (95% C.I. .67, .87, $p < .001$) and .77 (95% C.I. .67, .87, $p < .001$) respectively, indicating good diagnostic accuracy (Figure 8.1b).



a)



b)

Figure 8.2 ROC curves demonstrating the difference in trade off of sensitivity and specificity for aspirators when weak is classified as a) a pass b) a fail.

Table 8.14 Likelihood ratios (full cohort analysis)

		Prevalence of silent aspiration (pre-odds ratio)	*Likelihood Ratio of positive test results (LR+)*		*Likelihood Ratio of negative test results (LR-)*	
			LR+ (95% C.I.)	*Post-test probability (post test odds)*	*LR- (95% C.I.)*	*Post-test probability (post test odds)*
0.8	*pass vs. fail*	36% (0.55)	4.13 (1.79, 10.18)	69% (2.27)	0.62 (0.48, 0.83)	26% (0.34)
	with trace aspirators removed, pass vs. fail	29% (0.41)	5.50 (2.47, 12.77)	70% (2.28)	0.46 (0.30, 0.69)	16% (0.19)
0.6	*pass vs. fail*	36% (0.55)	3.3 (1.61, 6.71)	64% (1.79)	0.59 (0.43, 0.82)	25% (0.33)
	with trace aspirators removed, pass vs. fail	29% (0.41)	4.33 (2.23, 8.09)	64% (1.79)	0.39 (0.22, 0.65)	14% (0.16)
0.4	*pass vs. fail*	36% (0.55)	2.38 (1.49, 3.59)	57% (1.31)	0.43 (0.24, 0.71)	19% (0.24)
	with trace aspirators removed	29% (0.41)	2.91(1.89, 3.77)	55% (1.21)	0.21 (0.07, 0.49)	8% (0.09)

PART C: RELIABILITY STUDIES

CHAPTER NINE

STUDY III. INTRA- AND INTER-RATER RELIABILITY FOR JUDGEMENT OF COUGH FOLLOWING CITRIC ACID INHALATION- A PILOT STUDY [9]

9.1 Hypotheses and Rationale

Cough strength, in addition to cough sensitivity, has been linked with increased aspiration and pneumonia risk. Subjective voluntary cough judgement is relatively common in bedside CSE but its reliability has received little attention (Hypothesis 6.2).

9.2 Methodology

9.2.1 Participants.

The reliability study, including use of video recordings of patients who provided informed consent, was reviewed and approved by an appropriate regional ethics committee (Human Ethics Committee, University of Canterbury, HEC Application 2011.01.LRPS**)**. Participants included 11 SLTs who had received an eight-hour cough reflex testing training session and had been using cough reflex testing for one year (experienced raters) and 34 SLTs with no experience or formal training with the cough reflex test (inexperienced raters). Recruitment represented a convenience sample of clinicians attending a number of professional development events. The SLTs ranged in clinical experience from new graduate to specialist and all reported working with adults with dysphagia.

[9] *Miles, A. & Huckabee, M-L. (2013) Intra and inter-rater reliability for judgement of cough following citric acid inhalation. International Journal of Speech-Language Pathology, 15 (2), 209-215.*

9.2.2 Materials.

Informed consent for videotaping was secured from ten hospitalized adults (mixed gender, age range 24-91 years) at two urban hospitals to provide the data for reliability analysis. The videos represented 10 patients consecutively referred for swallowing assessments. Patient aetiology included progressive neurological disease, acute stroke, and frail elderly. Cough strength was not objectively assessed but the 10 patients were considered by consensus of the researchers to be representative of the range of responses seen in a hospital setting. Non-dysphagic patients were not selected so that the videos represented an 'average' caseload. Patients were video-recorded using a Mino HD flip video camera (CISCO, Irvine, CA) while undergoing a cough reflex test as part of their standard dysphagia assessment. The ten video clips were edited into a three-minute high-resolution movie using iMovie (Apple, Cupertino, CA). Each clip showed a patient receiving one 15-second dose of nebulised citric acid solution (diluted in 0.9% sodium chloride) through a facemask using a PulmoMate Compressor/Nebuliser (model 4650I) (DeVilbiss Healthcare LLC, Pennsylvania, US). This movie was labelled 'First Viewing'. The movie was then recreated, showing the same ten video clips in a randomly different order and labelled 'Second Viewing'.

9.2.3 Data collection protocol.

Participants viewed the movies through Windows Media Player via projector onto a conference room screen. Participants were asked to independently rate the cough response seen in each video clip as strong (2 or more strong coughs), weak (2 or more weak coughs) or absent (1 or no coughs). The C2 scoring system was chosen for this study (Morice et al., 2007). This system requires a response of two coughs within 15 seconds of presentation of tussive stimuli and is recommended by the European Respiratory Society (ERS) Guideline for

Assessment of Cough (Morice et al., 2007). Participants were given no specific definition of a cough, but were told that a throat clear is not considered a cough response. They were provided with no further education about cough or cough strength judgement. After watching the 'First Viewing' of the movie they were given a 15-minute break where participants were discouraged from discussing the videos. They were then asked to watch the 'Second Viewing' of the movie. After the second viewing, participants were encouraged to discuss their experience of judging the videos with each other and the researchers.

9.2.4 Data analysis.

Data were analysed using SPSS version 20 (SPSS, Chicago, IL, USA). Fleiss' generalized kappa measurement of agreement for multiple raters when assigning categorical ratings was used. The data from experienced raters and inexperienced raters were analysed as separate groups. Numerical coding for the three categories was defined as: strong (2), weak (1) and no cough (0). Additionally, within each group, each category was separately analysed for agreement. The Landis & Koch interpretation of Fleiss' generalized kappa values was used (Landis & Koch, 1977). Descriptive data from the unstructured discussion between participants following completion of the viewings were collected. Using the theory of qualitative analysis, the individual comments were divided into meaning units and themes were derived (Graneheim & Lundman, 2004). This study was considered a pilot study and no power calculation was completed.

9.3 Results

The raw agreement data for all raters for first viewing and second viewing are presented in Table 9.1 and Table 9.2. The inexperienced raters displayed an overall agreement of 69% (range across videos 47-97%) for the first viewing and 72% (range across

videos 50-97%) for the second viewing. In comparison, the experienced raters displayed an overall agreement of 75% for both viewings (first viewing range 45-100%, second viewing range 55-100%) with three videos rated with 100% agreement in the second viewing.

9.3.1 Inter-rater reliability.

Inter-rater reliability for inexperienced raters for the first viewing was calculated at $\kappa = .36$ ($p < .001$, 95% C.I. .35, .38). For the second viewing, these raters achieved only a marginally greater $\kappa = .41$ ($p < .001$, 95% C.I. .39, .43). The experienced raters achieved a $\kappa = .46$ ($p < .001$, 95% C.I. .40, .52) across the first viewing. This was marginally greater for the second viewing of the videos with a $\kappa = .49$ ($p < .001$, 95% C.I. .43, .55). There were marked differences in agreement between categories for both groups on both viewings. A summary of overall agreement is presented in Table 9.3, including κ-values, standard error values and 95% confidence intervals. Across both groups, agreement for strong cough ranged from $\kappa = .38$ to .49, weak cough agreement ranged from $\kappa = .08$ to .29 and absent cough agreement ranged from $\kappa = .63$ to .70. Confidence intervals for category agreement were wide, likely secondary to the small data set once the 10 items were analysed separately as three categories.

Table 9.1 Raw agreement data (first viewing)

	Experienced Raters				*Inexperienced Raters*			
	absent	*weak*	*strong*	***% Agreement***	*absent*	*weak*	*strong*	***% Agreement***
Video 1	0	1	10	**90**	0	12	22	**65**
Video 2	0	10	1	**90**	2	16	16	**47**
Video 3	0	7	4	**63**	0	12	22	**65**
Video 4	8	2	1	**73**	20	14	0	**59**
Video 5	2	5	4	**45**	4	8	22	**65**
Video 6	0	6	5	**55**	0	12	22	**65**
Video 7	0	2	9	**82**	1	11	22	**65**
Video 8	7	4	0	**64**	20	14	0	**65**
Video 9	10	1	0	**91**	31	2	1	**92**
Video 10	11	0	0	**100**	33	1	0	**97**
Mean Agreement				**75**				**69**

Table 9.2 Raw agreement data (second viewing)

	Experienced Raters				*Inexperienced Raters*			
	absent	*weak*	*strong*	***% Agreement***	*absent*	*weak*	*strong*	***% Agreement***
Video 1	0	0	11	**100**	0	5	29	**85**
Video 2	0	7	4	**64**	0	18	16	**53**
Video 3	0	7	4	**64**	1	16	17	**50**
Video 4	7	4	0	**64**	28	6	0	**82**
Video 5	1	4	6	**55**	4	7	23	**68**
Video 6	0	4	7	**64**	0	16	18	**53**
Video 7	0	3	8	**73**	0	9	25	**73**
Video 8	4	7	0	**64**	22	12	0	**65**
Video 9	11	0	0	**100**	31	3	0	**92**
Video 10	11	0	0	**100**	33	1	0	**97**
Mean Agreement				**75**				**72**

Table 9.3 Overall agreement and category specific agreement

		Kappa	*Standard error*	*p value*	*Lower 95% confidence limit*	*Upper 95% confidence limit*
Experienced raters (N: 34), viewing 1	***overall agreement***	**.46**	**.03**	**<. 001**	**.40**	**.52**
	strong cough rating	.43	.15	.003	.13	.73
	weak cough rating	.270	.16	.052	.05	.59
	absent cough rating	.68	.16	<. 001	.36	1.00
Experienced raters (N: 34), viewing 2	***overall agreement***	**.49**	**.03**	**<. 001**	**.43**	**.55**
	strong cough rating	.49	.16	<. 001	.18	.80
	weak cough rating	.29	.17	.044	.03	.62
	absent cough rating	.69	.16	<. 001	.38	1.00
Inexperienced raters (N: 11), viewing 1	***overall agreement***	**.36**	**.009**	**<. 001**	**.35**	**.38**
	strong cough agreement	.38	.09	<. 001	.20	.55
	weak cough agreement	.07	.08	.192	.08	.22
	absent cough agreement	.63	.08	<. 001	.48	.79
Inexperienced raters (N: 11), viewing 2	***overall agreement***	**.41**	**.009**	**<. 001**	**.39**	**.43**
	strong cough agreement	.40	.09	<. 001	.23	.57
	weak cough agreement	.08	.07	.122	.06	.22
	absent cough agreement	.70	.08	<. 001	.53	.87

9.3.2 Intra-rater reliability.

Intra-rater reliability was higher than inter-rater agreement with a $\kappa = .62$ ($p < .001$, 95% C.I. .54, .69) for inexperienced raters and a $\kappa = .70$ ($p < .001$, 95% C.I. .57, .81) for experienced raters. Again, differences in agreement across categories were seen. Intra-rater agreement for inexperienced raters ranged from: strong $\kappa = .66$ ($p < .001$, 95% C.I. .37, .95), weak $\kappa = .41$ ($p < 0.001$, 95% C.I. .13, .69), no cough $\kappa = .76$ ($p < .001$, 95% C.I. .48, 1.00). Experienced raters intra-rater agreement ranged from: strong $\kappa = .71$ ($p < .001$, 95% C.I. .21, 1.00), weak $\kappa = .58$ ($p = .012$, 95% C.I. .07, 1.00), no cough $\kappa = .82$ ($p < .001$, 95% C.I. .31, 1.00).

9.3.3 Descriptive data.

A list of qualitative responses is presented in Table 9.4. The raters' responses were separated into three themes i) definition of cough ii) definition of weak cough iii) practice/ confidence. Participants discussed uncertainty in the definition of cough "he looked like he was coughing but I don't know", the definition of a weak cough "he looks very frail, does that make him weak?" and voiced increase in confidence between viewings "I had a better idea about what I was going to rate as a cough the second time".

Table 9.4 Themes of qualitative data with representative examples of comments

Definition of a cough	*Definition of a weak cough*	*Practice/ Confidence*
"I decided to close my eyes and just listen for the sound of a cough as the picture confused me"	"That was much harder than I thought it would be, I think I judge it on the person's general strength clinically, not their cough".	"It felt a lot easier the second time around"
"He looked like he was coughing but I don't know"	"What is a weak cough… all my patients are weak?"	"I remember when I first started using the cough reflex test, I was confused by weak vs. strong but now that it is something I focus on more, I feel more confident"
"What is a cough?"	"I don't know… he didn't cough as strong as I can but it seemed strong enough for his age"	"I don't think I thought about cough strength before I started using the cough reflex test"
"His shoulders moved but I didn't know if was a cough or not…I thought I'd just need to count the coughs but it was more complicated than that!"	"He looked so weak…it had to be a weak"	
"What is the difference between a throat clear and a cough?"		

CHAPTER TEN

STUDY IV. INTER-RATER RELIABILITY FOR JUDGEMENT OF COUGH FOLLOWING CITRIC ACID INHALATION AFTER TRAINING [10]

10.1 Hypotheses and Rationale

Measuring the strength of reflexive cough provides valuable information about a patient's ability to protect the airway from aspirated material. The reliability of subjective cough judgements by SLTs has received little research attention. There is minimal formal training in cough physiology in undergraduate SLT programmes and no research on the effect of specific training on cough judgement (Hypothesis 6.3).

10.2 Methodology

10.2.1 Participants.

The reliability study, including use of video recordings of patients who provided informed consent, was reviewed and approved by an appropriate regional ethics committee (Human Ethics Committee, University of Canterbury, HEC Application 2011.01.LRPS**)**. Recruitment, consent and participation took place at a number of professional development events in New Zealand, Australia, UK, Ireland and USA.

10.2.2 Materials.

Informed consent for videotaping was secured from ten hospitalised adults (mixed gender, age range 59-91 years) at two urban hospitals to provide the data for reliability

[10] *Miles, A., McFarlane, M. & Huckabee, ML. (in review) Intra and inter-rater reliability for judgement of cough following citric acid inhalation with training. Dysphagia. Submitted 2nd August 2013.*

analysis. The strength of patients' coughs was not objectively assessed but the ten patients were considered by consensus of the authors to be representative of the range of responses seen in a hospital setting. Eight videos of patients with dysphagia were selected from 15 consecutive swallowing assessments. Patient aetiology included progressive neurological disease, acute stroke, frail elderly and orthopaedic. Two elderly non-dysphagic patients were selected from a non-neurological ward to ensure that the videos included a representative example of a normal elderly cough. Patients were video-recorded using a Mino HD flip video camera (CISCO, Irvine, CA) while undergoing a cough reflex test. The ten video clips were edited into a three-minute high-resolution movie using iMovie (Apple, Cupertino, CA). Each clip showed a patient receiving one 15-second dose of nebulised citric acid solution (diluted in 0.9% sodium chloride) through a facemask using a PulmoMate Compressor/Nebuliser (model 4650I) (DeVilbiss Healthcare LLC, Pennsylvania, US).

10.2.3 Protocol.

Participants were given a 2-hour training session. This included an introduction to the use of cough reflex testing in dysphagia assessment, including rationale and protocols. A summary of cough physiology was provided including definitions of cough and cough strength. They were provided with videotaped examples of strong, weak and absent coughs and were encouraged to make subjective judgements and discuss their clinical reasoning leading to those judgements. The definition for weak cough suggested to participants was "a cough that does not appear strong enough to clear aspiration and is substantially weaker than their own reflexive cough."

Participants viewed the movie through Windows Media Player via a data projector onto a conference room screen. Participants were asked to independently rate the cough response seen in each video clip as i) present (2 or more coughs) or absent (1 or no coughs);

if the cough was present, they then rated the response as ii) strong (2 or more strong coughs) or weak (2 or more weak coughs). The C2 scoring system was chosen for this study (Morice et al., 2007). This system requires a response of two coughs within 15 seconds of presentation of tussive stimuli and is recommended by the European Respiratory Society (ERS) Guideline for Assessment of Cough (Morice et al., 2007). After the viewing, participants were asked to write any qualitative comments about their experience in interpreting the videos. They also provided their years of experience in working with patients with dysphagia, their primary caseload, any previous training or clinical experience in cough reflex testing and any hearing or visual impairments.

10.2.4 Data analysis.

Data were analysed using SPSS version 20 (SPSS, Chicago, IL, USA). Fleiss' generalized kappa measurement of agreement for multiple raters when assigning categorical ratings was used. Two sets of numerical coding were made for each of the two ratings. The first rating was directed at presence of cough: cough (1), no cough (2). While the second rating considered cough strength: strong cough (1), weak cough (2) and no cough (3). Within each group, each category was separately analysed for agreement. Finally, videos where absent cough was predominately rated were then removed and the remaining six videos were numerically coded as strong (1) or weak cough (2) and analysed separately to exclusively assess the agreement of strength. Confidence intervals and standards errors are reported. The Landis & Koch interpretation of Fleiss' generalized kappa values was used (Landis & Koch, 1977). Data were separated by experience level to assess the effect of years of experience in working with patient with dysphagia and experience in cough reflex testing on agreement. Written qualitative comments provided by participants following completion of the viewings were collated and transcribed. Using the theory of qualitative

analysis, the individual comments were divided into meaning units and themes were derived (Graneheim & Lundman, 2004). With an estimated proportion of positive ratings of .50, a minimal sample size of 15 raters per experience group was calculated to detect a standard error of 0.13 (Reichenheim, 2004; Sim & Wright, 2005).

10.3 Results

Participants included a convenience sample of 58 SLTs with an average of nine years of dysphagia experience (range 0-32 years, SD 7.7) (Table 10.1). All reported currently working with adults with dysphagia and all reported primarily working with a neurological population except one who had a predominantly otorhinolaryngology caseload. Nine clinicians from a single workplace reported using cough reflex testing routinely in their clinical practice. One participant reported a hearing impairment in one ear; no visual impairments were reported.

Table 10.1 Participants' levels of experience

	UK	*NZ*	*Australia*	*USA*	*Ireland*
Number of participants	19	9	12	8	10
% of participants with over 5 years experience	84%	56%	50%	88%	70%
% of participants using CRT	0%	100%	0%	0%	0%

The raw agreement data for all raters are presented in Table 10.2. Raters displayed an overall agreement of 91% (range across videos 64-100%) for cough presence and 82% (range across videos 55-97%) for cough strength.

Table 10.2 Raw agreement data for full cohort

	Cough Presence			*Cough Strength*			
	absent	*present*	*% agreement*	*strong*	*weak*	*absent*	*% agreement*
Video 1	42	16	72	0	16	42	72*
Video 2	0	58	100	55	3	0	95
Video 3	37	21	64	00	21	37	64*
Video 4	0	58	100	11	47	0	81
Video 5	0	58	100	10	48	0	83
Video 6	0	58	100	55	3	0	95
Video 7	0	58	100	26	32	0	55
Video 8	45	13	78	0	13	45	78*
Video 9	58	0	100	0	0	58	100*
Video 10	0	58	100	56	2	0	97
Mean Agreement			91%				82%

** data report agreement for absence rather than strength*

10.3.1 Inter-rater reliability.

Inter-rater reliability for cough presence was calculated at $\kappa = .71$ ($p < .001$ 95% C.I. .70, .73) and for cough strength at $\kappa = .61$ ($p < .001$ 95% C.I. .60, .62). A summary of overall agreement and category specific agreement is presented in Table 10.3 including κ-values, p values, standard errors and 95% C.I.s. Agreement for weak cough was poorer ($\kappa = .40$, $p < .001$, 95% CI .28, .52) than strong cough ($K= .70$, $p <.001$, 95% C.I. .58, .83) and absent cough ($\kappa = .71$, $p < .001$, 95% C.I. .60, .83). When raters with practical cough reflex testing experience were removed from analysis, cough strength agreement decreased to $\kappa = .68$ ($p < .001$, 95% C.I. .67, .70) and cough strength judgement decreased to $\kappa = .57$ ($p < .001$, 95% C.I. .56, .58).

When videos judged predominately as ‘no cough’ were removed from analysis (Video 1, 3, 8 and 9), strength judgement agreement was poorer with inter-rater reliability for cough strength at $\kappa = .52$ ($p < .001$, 95% C.I. .47, .53) (Table 10.4).

10.3.2 Experience levels.

Raw data and agreement levels for cough presence and cough strength based on experience levels are presented in Table 10.5 and Table 10.6 respectively. Agreement of cough presence was, according to the Landis and Koch classification, substantial for those with CRT experience ($\kappa = 1.0$, 95% C.I. 1.00, 1.00) and stronger for those with less clinical dysphagia experience ($\kappa = .78$, $p < .001$, 95% C.I. .73, .84) than those with more clinical dysphagia experience ($\kappa = .68$, $p < .001$, 95% C.I. .66, .71) (Table 10.3). Cough strength agreement was also ‘substantial’ for those with CRT experience ($\kappa = .87$, 95% C.I. .55, 1.00) but moderate for both inexperienced ($\kappa = .39$, $p < .001$, 95% C.I. .17, .61) and experienced clinicians ($\kappa = .40$, $p < .001$, 95% C.I. .26, .54) (Table 10.3). Overlapping confidence intervals should be taken into account in this interpretation. Wide confidence intervals (due to small sample sizes) for the under 5 years experience cohort and cough reflex testing experience cohort should also be considered.

Table 10.3 Overall agreement and category specific agreement

		Kappa	*p value*	*Standard error*	*Lower 95% confidence limit*	*Upper 95% confidence limit*
All participants (N: 58)	***overall agreement presence***	**.71**	**< .001**	**.008**	**.70**	**.73**
	overall agreement strength	**.61**	**< .001**	**.006**	**.60**	**.62**
	strong cough rating	.70	< .001	.065	.58	.83
	weak cough rating	.40	< .001	.059	.28	.52
	absent cough rating	.71	< .001	.058	.60	.83
Participants with over 5 years dysphagia experience (N: 41)	***overall agreement presence***	**.68**	**< .001**	**.011**	**.66**	**.71**
	overall agreement strength	**.60**	**< .001**	**.008**	**.58**	**.61**
	strong cough rating	.71	< .001	.078	.56	.86
	weak cough rating	.40	< .001	.073	.26	.54
	absent cough rating	.68	< .001	0.69	.55	.82
Participants with under 5 years dysphagia experience (N: 17)	***overall agreement presence***	**.78**	**< .001**	**.027**	**.73**	**.84**
	overall agreement strength	**.62**	**< .001**	**.019**	**.59**	**.66**
	strong cough agreement	.68	< .001	.132	.43	.94
	weak cough agreement	.39	< .001	.112	.17	.61
	absent cough agreement	.77	< .001	.122	.53	1.00

Participants with cough reflex testing experience (N: 9)	***overall agreement presence***	**1.0**	**< .001**	**.053**	**1.00**	**1.00**
	overall agreement strength	**.92**	**< .001**	**.038**	**.85**	**1.00**
	strong cough agreement	.89	< .001	.185	.53	1.00
	weak cough agreement	.87	< .001	.166	.55	1.00
	absent cough agreement	1.0	< .001	.206	.60	1.00
All participants except those with cough reflex testing experience (N: 49)	***overall agreement presence***	**.68**	**< .001**	**.009**	**.67**	**.70**
	overall agreement strength	**.57**	**< .001**	**.007**	**.56**	**.58**
	strong cough agreement	.68	< .001	.072	.54	.82
	weak cough agreement	.35	< .001	.066	.22	.48
	absent cough agreement	.68	< .001	.061	.56	.80

Table 10.4 Overall agreement for strength rating with absent cough videos removed from analysis

	Kappa	*p value*	*Standard error*	*Lower 95% confidence limit*	*Upper 95% confidence limit*
All participants (N: 58)	**.52**	**< .001**	**.010**	**.50**	**.54**
Participants with over 5 years dysphagia experience (N: 41)	.50	< .001	.014	.47	.53
Participants with under 5 years dysphagia experience (N: 17)	.47	< .001	.035	.40	.54
Participants with cough reflex testing experience (N: 9)	.38	< .001	.068	.25	.51
Participants without cough reflex testing experience (N: 49)	.46	< .001	.012	.44	.49

Table 10.5 Raw agreement data for cough presence categorised by experience level

	Cough Presence								
	absent			*present*			*% agreement*		
	under 5 yrs	*over 5 yrs*	*CRT use*	*under 5 yrs*	*over 5 yrs*	*CRT use*	*under 5 yrs*	*over 5 yrs*	*CRT use*
Video 1	14	28	9	3	13	0	82	68	100
Video 2	0	0	0	17	41	9	100	100	100
Video 3	12	25	9	5	16	0	71	61	100
Video 4	0	0	0	17	41	9	100	100	100
Video 5	0	0	0	17	41	9	100	100	100
Video 6	0	0	0	17	41	9	100	100	100
Video 7	0	0	0	17	41	9	100	100	100
Video 8	15	30	9	2	11	0	88	73	100
Video 9	17	41	9	0	0	0	100	100	100
Video 10	0	0	0	17	41	9	100	100	100
Mean Agreement							**94%**	**92%**	**100%**

Table 10.6 Raw agreement data for cough strength categorised by experience level

	Cough Strength											
	absent			*strong*			*weak*			*% agreement*		
	under 5 yrs	*over 5 yrs*	*CRT use*	*under 5 yrs*	*over 5 yrs*	*CRT use*	*under 5 yrs*	*over 5 yrs*	*CRT use*	*under 5 yrs*	*over 5 yrs*	*CRT use*
Video 1	14	28	9	0	0	0	3	13	0	82	68	100*
Video 2	0	0	0	16	39	9	1	2	0	94	95	100
Video 3	11	25	9	0	0	0	6	16	0	65	61	100*
Video 4	0	0	0	3	8	0	14	33	9	82	80	100
Video 5	0	0	0	3	7	2	14	34	7	82	83	100
Video 6	0	0	0	16	39	9	1	2	0	94	95	100
Video 7	0	0	0	10	16	0	7	25	9	59	61	66
Video 8	15	30	9	0	0	0	2	11	0	88	73	100*
Video 9	17	41	9	0	0	0	0	0	0	100	100	100*
Video 10	0	0	0	16	40	9	1	1	0	94	98	100
Mean Agreement										**84%**	**81%**	**96%**

* figures report agreement for absence rather than strength

10.3.3 Descriptive data.

Qualitative comments given by participants were again divided into four themes. In this study, themes included: the training, using cues, uncertainty around the subjectivity of strength and uncertainty around cough presence (Table 10.7). Participants were positive about the training and described cues they used in their ratings. As in Study III, uncertainty about the subjectivity of strength was the most frequent comment with 15 participants commenting on it.

Table 10.7 Themes of qualitative data with representative examples of written comments

The training	*Using cues*	*Uncertainty around subjectivity of strength*	*Uncertainty around cough presence*
"Really good opportunity to train clinicians in cough strength"	"I was influenced by visually seeing the patient e.g., if the patient appeared weak and unwell or looked strong"	"I wonder if there should be a middle point between strong and weak"	"Some do a double cough 2 in 1, not sure if it's counted as 2 coughs"
"The training helped me to be strict in determining strength"	"Lateral view was easier I could see the chest more"	"Absent vs. present easy"	"Difficult rating a cough as absent when subject makes a physical movement but it's not accompanied by an explosive sound"
"Interpreting the videos made me realize how subjective my clinical judgements can be especially strong vs. weak"	"I tried not to look, just listen"	"Strong/ weak very subjective"	"The first video was hard as I couldn't hear a response but they were moving"

"I don't feel I know enough about cough now… weak, chesty, wheezy"	"Video clip 3 was hard, I couldn't see the face"	"I found I put weak if it wasn't strong rather than knowing what weak looked like"
"It would have been good to see more videos beforehand"		"As an acute clinician, definition of weak differs i.e., low expectations of what is strong"

PART D: RANDOMISED CONTROLLED TRIAL

CHAPTER ELEVEN

STUDY V. CLINICAL IMPLICATIONS OF COUGH REFLEX TESTING IN DYSPHAGIA MANAGEMENT FOLLOWING STROKE: A RANDOMISED CONTROLLED TRIAL [11]

11.1 Hypothesis and Rationale

Significant health issues and service delivery costs are associated with post-stroke pneumonia related to dysphagia. Although the development of pneumonia is known to be multi-factorial, silent aspiration (aspiration without a cough response) has been linked to increased prevalence of pneumonia and mortality. There is increasing evidence of the clinical utility of CRT for identifying silent aspiration and reducing pneumonia following stroke (Hypothesis 6.4).

11.2 Methodology

11.2.1 Patient selection.

Three hundred and eleven acute stroke patients (165 females, 146 males) consecutively referred to SLT for swallowing assessment were recruited from four urban hospitals. At all four hospitals, patients were referred following a failed nurse-administered dysphagia screen. For details of recruitment see Figure 11.1. Patients were excluded if palliative swallowing advice was requested rather than active treatment, as these patients do not routinely receive full assessment protocols and pneumonia is not actively prevented. The

[11] *Miles, A., Zeng, I.S.L, McLauchlan, H. & Huckabee, ML. (2013) Cough reflex testing in dysphagia following stroke: A randomized controlled trial. Journal of Clinical Medicine Research; 5 (3), 222-233.*

patients' ages ranged from 22-102 years (mean of 78 years, SD 13.5). Initial CT scans classified lesions as follows: 212 cortical, 48 subcortical, 8 brainstem, 12 cerebellar, 8 multi-level, 5 small vessel disease, and 18 with no new abnormalities detected on CT scan.

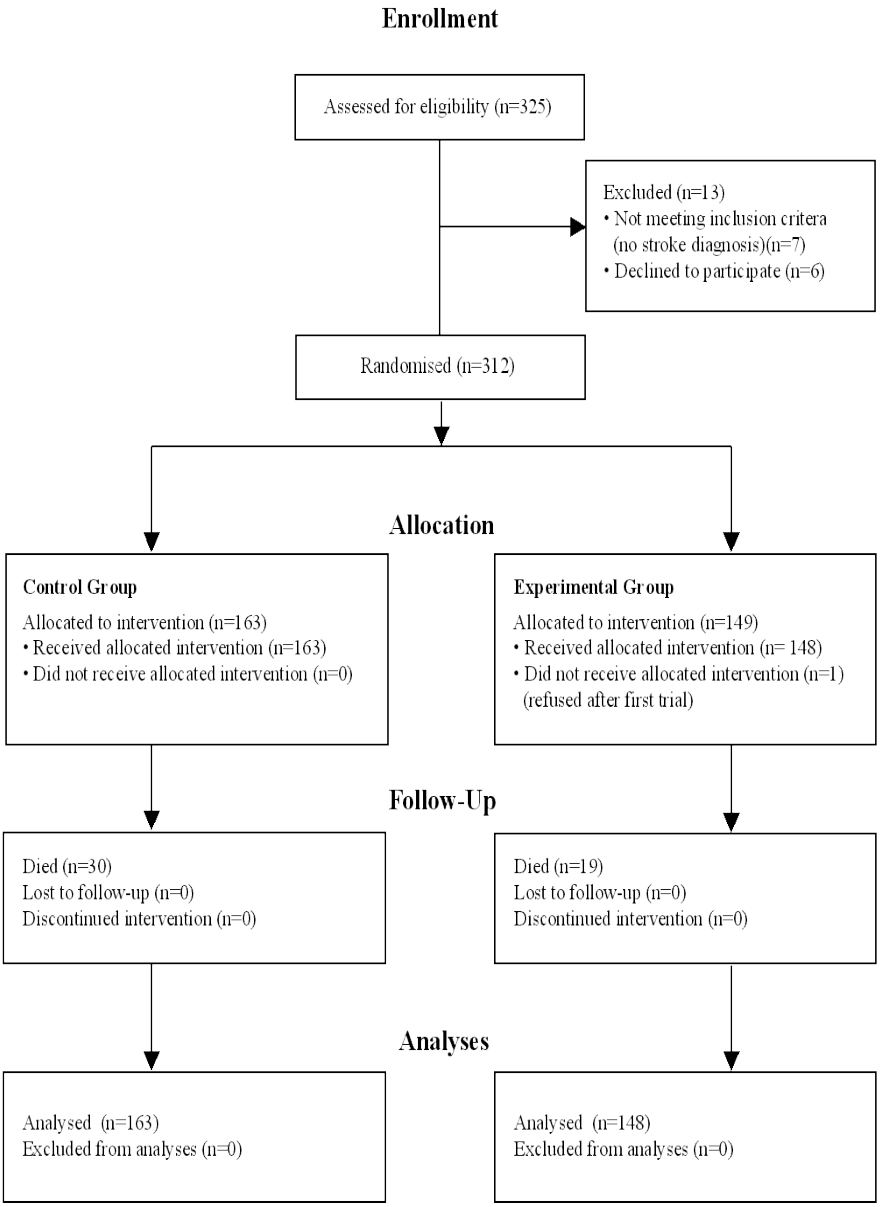


Figure 11.1 Clinical trial patient allocation

11.2.2 Study design.

This study received appropriate national ethics approval (Northern Y Regional Ethics Committee NTY/09/11/113) and individual site approval at each of the four hospitals. All participants gave informed consent independently or consent was gained by proxy. Participants were randomly assigned to the control group or the experimental group based on a simple randomisation procedure using one computer generated random numbers list held in the research office remote from the study environments. Participating clinicians at each research site telephoned the research office after gaining consent from each patient and were immediately given a randomisation assignment to either the control group or the experimental group. The non-blinded study design was unavoidable for patients, the ward clinicians, multidisciplinary team and the researcher collecting the outcome data. It was essential that the results of the cough reflex test were incorporated into management decisions in order to translate to change in outcomes. Documentation of cough reflex test results in a patient's clinical notes was therefore an integral component of the protocol. The research office providing the randomisation code was blinded to research site, clinician and any patient details. Clinicians who recruited, assessed and treated the participants in the study received eight hours of formal teaching regarding CRT procedures and interpretation, as well as the opportunity for reflection in practice on a regular basis throughout the recruitment period. Protocols, procedural flow charts and management guidelines were provided.

11.2.3 Protocol.

For those in the control group, CSE was executed as defined by local clinical protocols. At all sites, this involved a case history, cognitive/communication screen, cranial nerve examination and observation of oral ingestion of foods and fluids. For patients in the

experimental group, the standard evaluation was augmented with the inclusion of CRT prior to any oral trials. Citric acid solutions diluted in 0.9% sodium chloride were prepared by each hospital pharmacy on a weekly basis. These included a lower dose of 0.8mol/L at which 92.5% of healthy individuals produced a natural cough and a higher dose of 1.2mol/L at which 80% of healthy individuals were no longer able to suppress a cough (Monroe et al., 2010). CRT was administered using a PulmoMate Compressor/Nebuliser (model 4650I) (DeVilbiss Healthcare LLC, Pennsylvania, US) with a predetermined free-flow output of 8 litres per minute and a restricted flow output of 6.6 litres per minute. A facemask method was used (Figure 7.2), as was described in prior research (Wakasugi et al., 2008) and utilised in establishing normative data on which this study was based (Monroe et al., 2010).

Figure 11.2 Cough reflex testing equipment

Patients were told that they were participating in a cough test and they were asked to cough "if they felt the need to cough". Initially a placebo of 0.9% NaCl without citric acid was presented to coach the participant on task completion. Presence or absence of cough during a 15-second delivery period was documented. Cough response was considered positive if two or more coughs were triggered (C2 response threshold) as recommended by

the ERS Task Force (Morice et al., 2007). The test was repeated three times at the low concentration, with a 30-second interval between each inhalation to prevent tachyphylaxis (Morice et al., 2007). If a patient coughed on this initial test, the clinician then asked the patient to "try to suppress the cough as much as you can" while the same low dose was administered. If they were able to suppress a cough at 0.8mol/L (2 out of 3 trials), the higher concentration was administered (1.2mol/L). The suppressed cough test was passed when participants coughed on at least two out of three trials of that dose. Absence of a natural cough at 0.8mol/L or the ability to suppress a cough at the higher dose was considered a failed test (Figure 11.3). If the patient passed the suppressed cough test, clinicians were also asked to subjectively judge whether the cough response was strong or weak.

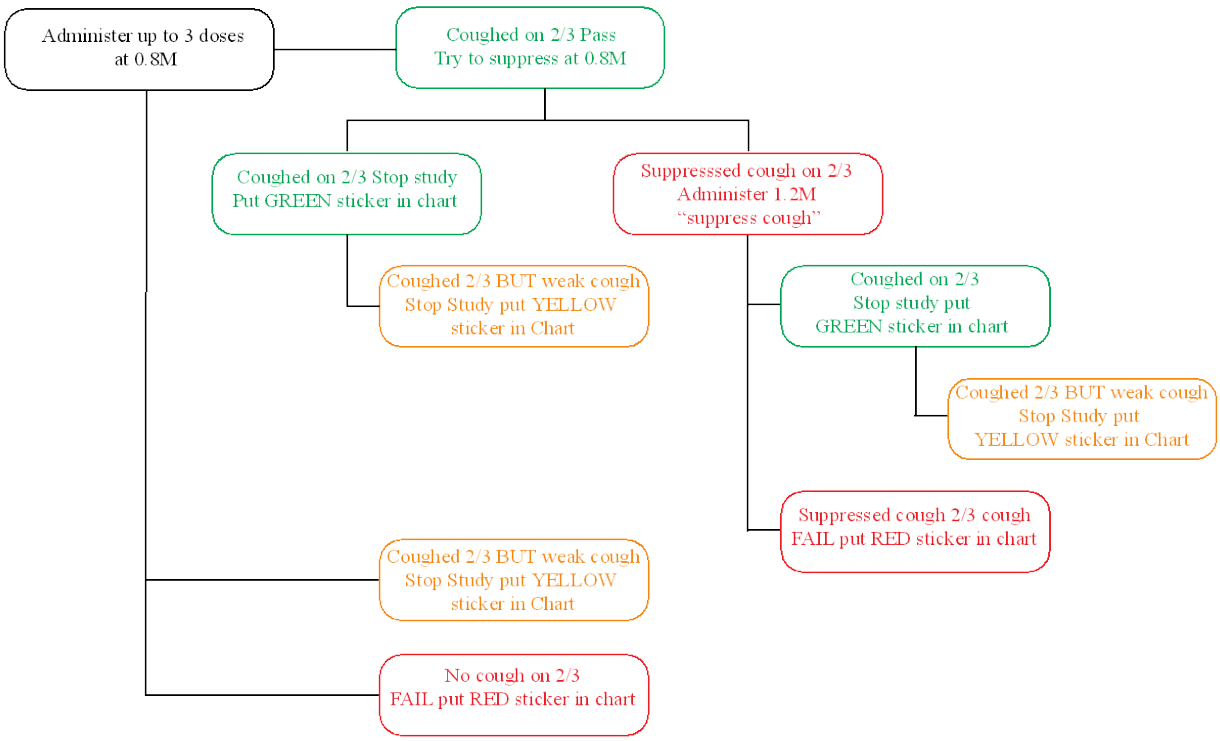


Figure 11.3 Flow chart of CRT procedure provided to SLTs during recruitment period

Subsequent management decisions were not prescribed, but were left to the judgment of the treating clinician. In the control group, clinicians were encouraged to follow their standard clinical decision making processes. In the experimental group, clinicians were encouraged to incorporate the combined results of the CSE and the CRT into multidisciplinary dysphagia management such as dietary recommendations, instrumental assessment referrals, compensatory and rehabilitation approaches. Multidisciplinary information sheets and training sessions were used to support carryover of a treatment plan. Stickers containing information for the multidisciplinary team were placed in patients' clinical notes (Figure 11.4). If the patient failed the CRT, the team was advised that s/he may not show overt signs of aspiration and would be at high risk of aspiration pneumonia. If the patient presented with a weak cough, the team was advised that the patient has a cough response, but that if the patient coughed, the cough may not be sufficient to clear aspiration. When a patient passed the CRT, the multidisciplinary team was advised that the patient was likely to show overt signs of aspiration if s/he was aspirating and therefore had a better chance of protecting the airway if they aspirated.

11.2.4 Outcome measures

The primary outcome measure was the proportion of patients with confirmed pneumonia within three months post stroke using the criteria described by Mann and colleagues where three or more of the following variables constitute a diagnosis: fever (>38°C), productive cough with purulent sputum, abnormal respiratory examination [tachypnea (>22/min), tachycardia, inspiratory crackles, bronchial breathing], abnormal chest radiograph, arterial hypoxemia (PO2 <70 mm Hg), and isolation of a relevant pathogen (positive gram stain and culture) (Mann et al., 1999). A distinction between pneumonia and aspiration pneumonia was not attempted. Secondary patient outcome measures included

length of acute hospital stay in days and the percentage of patients with readmissions for chest infection within three months post recruitment to the study. Clinical decision parameters were also collected, including percentage of patients with completed VFSS or FEES during acute admission or three month post evaluation (i.e., change in frequency in referral rates with addition of CRT) and route and type of intake at three month review using the Functional Oral Intake Scale (FOIS) (Crary, Carnaby-Mann, & Groher, 2005). Outcomes were assessed via phone call with patients, next-of-kin, residential care staff and/or general practitioners and a chart review at three months post recruitment.

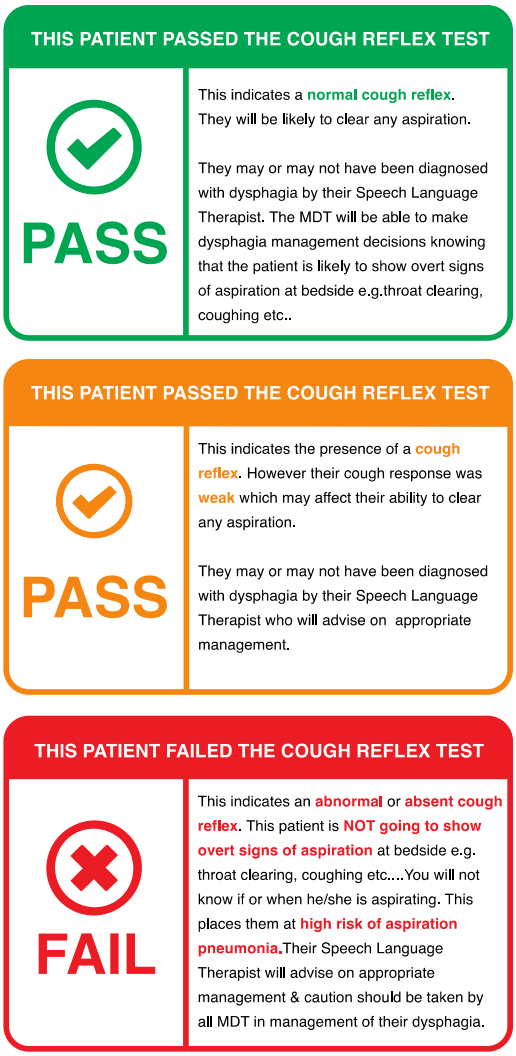


Figure 11.4 Stickers placed in clinical notes after completing a cough reflex test

11.2.5 Data analysis

Statistical analyses were completed using SAS version 9.3 (SAS, Cary, NC, USA) and SPSS version 20 (SPSS, Chicago, IL, USA). A two-sample t-test was used to compare the mean length of stay (LOS) between the control group and experimental group; data were log transformed for analysis due to skewed distribution. Welch's analysis of variance for groups with unequal variance was used for comparing the diets between experimental group and control group. Chi square test was used to assess the associations between categorical data outcomes between control and experimental groups. Exact Cochran-Armitage Trend Test was used to assess the associations between mortality, pneumonia, readmission and the CRT results. Multiple logistic regressions were applied to evaluate the efficacy of the cough reflex test adjusted by confounding variables (gender, site, ACE inhibitors, cardiac comorbidities, previous stroke history, respiratory comorbidities, instrumental assessment and lesion locations), and the two-way interactions including CRT and cardiac comorbidities, CRT and previous stroke history, CRT and respiratory comorbidities, CRT and lesion locations, CRT and sites.

The model selections used Akaike information criterion (AIC). Firstly the full model with all confounding factors was fit, and a backward selection with AIC were used to select the main effect model. The two-way interactions were then added to the main effect model one by one for the final model. All analyses were based on intention-to-treat principle. An *a priori* minimal sample size of 268 participants (134 per experimental group) was calculated for an estimated effect size of 0.4 at the 0.05 significance level to achieve 90% statistical power.

11.2.6 Clinician survey.

Following the completion of patient recruitment, all participating health professionals (recruiting SLTs, Allied Health managers, stroke unit nursing and medical staff) were sent a written survey. The anonymous survey was a combination of forced choice and open questions. The survey inquired about their experience during the clinical trial, the effect of CRT on their clinical practice, their opinions on continuing use of CRT, and their perceived impact of CRT on patients' outcomes. Answers to forced choice questions were tallied for analysis. Qualitative comments provided by participants in open questions were collated. Using the theory of qualitative analysis, the individual comments were divided into meaningful units and themes were derived (Graneheim & Lundman, 2004).

11.3 Results

One hundred and sixty three patients were randomised to the control group. One hundred and forty eight patients were randomised to the experimental group. An analysis of baseline characteristics found no significant differences between groups except for a larger proportion of males in the experimental group (control 43%, experimental 53%, p = .053) (Table 11.1). Within the experimental group, 91 passed CRT with a strong cough (61%), 31 passed with a weak cough (21%) and 26 failed CRT (18%). There was variation across sites, especially with regards to the category of pass with a weak cough (range across sites, pass with strong cough = 56-69%, pass with weak cough = 6-33%, fail = 12-25%, $X^2 = 18.80$, p = .592). Although patients in both groups were referred to SLT with suspected swallowing difficulties, 45 (14%) patients were placed on a normal diet (FOIS 7) after the first assessment, 182 (59%) were placed on a full, modified diet (FOIS 4-6), and 84 (27%) were recommended to remain NBM or have oral trials only (FOIS 1-3). There was minimal

variation in diet recommendation across sites (range across sites, FOIS 1-3= 20-32%, FOIS 4-6= 57-63%, FOIS 7= 10-21%).

11.3.1 Reducing secondary complications.

A summary of outcome differences between the experimental group and control group are displayed in Table 11.2 and a summary of odds ratios for development of pneumonia and mortality between groups, adjusted for demographic and clinical factors, are displayed in Table 11.3. In the unadjusted and covariate-adjusted results, there were no significant differences in pneumonia rates between the control group and experimental group (unadjusted: control 21%, experimental 26%, $X^2 = 0.76$, p = .380; covariate-adjusted odds ratio: 1.7 (95% C.I. 0.9, 3.0, p = .100). There was a non-significant trend that pneumonia was associated with an adverse response on CRT (fail 35%, weak 32%, pass 21%, Z = 1.63, p = .112) with odds ratios of fail vs. pass 2.0 (95% C.I. 0.8, 5.2) and weak vs. fail 1.1 (95% C.I. 0.4, 3.4). Irrespective of randomisation, the variables of age, gender, hospital site, cardiac comorbidities and respiratory comorbidities were all associated with increased pneumonia risk and will be discussed in Study VI.

In the unadjusted and covariate-adjusted results, there were no significant differences in mortality rates in the experimental group compared with the control group (unadjusted: control 14%, experimental 20%, $X^2 = 2.11$, p = .151; covariate-adjusted odds ratio: 0.7 (95% C.I. 0.4, 1.3, p = 0.230). There was a non-significant trend that higher mortality was associated with adverse response on CRT (fail 23%, weak 16%, pass 10%, Z = 1.82, p = .071) with odds ratio of fail vs. pass 2.7 (95% C.I. 0.9, 8.5) and weak vs. fail 1.6 (95% C.I. 0.4, 5.8). Age and not taking ACE-inhibitors were associated with increased risk of mortality and will be discussed in Study VI.

Table 11.1 Demographic comparison between experimental group and control group

		Experimental Group (N=148)	*Control Group (N=163)*	*Association between Groups (p value)*
Demographics mean (SD)	*age*	76 (15)	79 (12)	.063
	male	78 (53%)	68 (42%)	.053
Ethnicity	*Caucasian*	111 (75%)	125 (77%)	.550
	Maori	16 (11%)	11 (7%)	
	Pacific Islander	13 (9%)	18 (11%)	
	other	8 (5%)	9 (6%)	
Hospital Site	*Hospital A*	43 (29%)	49 (30%)	.793
	Hospital B	37 (25%)	33 (20%)	
	Hospital C	52 (35%)	62 (38%)	
	Hospital D	16 (11%)	19 (12%)	
Comorbidities	*previous stroke history*	44 (30%)	46 (28%)	.769
	respiratory comorbidities	15 (10%)	26 (16%)	.089
	cardiac comorbidities	103 (70%)	116 (71%)	.762
Site of Lesion	*cortical*	102 (69%)	110 (67%)	.949
	subcortical	34 (23%)	34 (21%)	
	other	4 (3%)	9 (6%)	
	NAD	8 (5%)	10 (6%)	
Laterality of Lesion	*left*	69 (47%)	83 (51%)	.493
	right	64 (43%)	60 (37%)	
	other	15 (10%)	18 (11%)	
Diet after initial assessment mean (se) (13= non-oral feeding, 47= oral diets)		4.4 (0.2)	4.1 (0.2)	.180
Domicile on admission	*public hospital*	7 (5%)	6 (4%)	.650
	residential care facility	13 (9%)	19 (12%)	
	home	128 (86%)	138 (85%)	

Table 11.2 Outcome comparison between experimental group and control group

		Experimental Group	*Control Group*	*p value*
Domicile at 3 months post assessment	*public hospital*	12 (8%)	16 (10%)	.753
	residential care facility	64 (43%)	74 (45%)	
	home	72 (49%)	73 (45%)	
Mortality		20 (14%)	32 (20%)	.150
Confirmed pneumonia		38 (26%)	35 (21%)	.384
Readmission for pneumonia		7 (5%)	4 (2%)	.276
Diet at 3 months mean (se)		6.2 (0.1)	6.0 (0.1)	.218
Length of stay in acute ward median (IQR)		7 (5, 12)	6 (4.5, 11.5)	.582
Instrumental swallowing assessment completed		27 (18%)	12 (7%)	.004

There were no significant differences in length of stay, independence at three months and pneumonia readmissions to hospital between the two study groups (Table 11.2 & 11.3). Only one three-way interaction was found between CRT, respiratory comorbidities and pneumonia ($p = .043$) with lower pneumonia rates in those with respiratory comorbidities in the experimental group (5/15, 33%) compared with those with respiratory comorbidities in the control group (14/ 26, 54%).

11.3.2 Association of CRT result with other clinical factors.

There were no significant differences in age, gender, ethnicity, stroke history, cardiac comorbidities, stroke type or independence on admission across CRT results (Table 11.4). There was a significant difference in the incidence of respiratory comorbidities across CRT results with a larger proportion of patients with respiratory comorbidities having a weak CRT (fail 8%, weak 23%, pass 7%, $X^2 = 6.70$, $p = .044$).

Table 11.3 Multiple logistic regression analyses for pneumonia and mortality between two interventions groups adjusted by demographic and clinical factors

		Confirmed pneumonia odds ratio (95% confidence interval	*p value*	*Mortality odds ratio (95% confidence interval)*	*p value*
Received CRT vs. did not receive CRT		1.7 (0.9, 3.0)	.101	0.7 (0.4, 1.3)	.230
Age		1.4 (1.1, 1.9)	**.011**	1.7 (1.2, 2.3)	**.003**
Gender (male vs. female)		1.9 (1.0, 3.5)	**.042**	0.9 (0.5, 1.8)	.764
Study Sites	*Hospital A vs. Hospital C*	0.6 (0.3, 1.2)	.169	0.7 (0.3, 1.5)	.331
	Hospital B vs. Hospital C	0.4 (0.2, 0.9)	**.032**	0.8 (0.3, 1.8)	.509
	Hospital D vs. Hospital C	0.3 (0.09, 0.8)	**.021**	0.2 (0.05, 1.1)	.062
ACE inhibitors (not taking vs. taking)		1.6 (0.9, 3.1)	.127	2.7 (1.2, 5.8)	**.011**
Comorbidities	*cardiac*	3.0 (1.4, 6.5)	**.011**	1.9 (0.9, 4.2)	.124
	respiratory	4.3 (2.0, 9.1)	**< .001**	0.6 (0.2, 1.6)	.290
	previous stroke	1.8 (1.0, 3.3)	.074	1.4 (0.7, 2.8)	.348
Site of lesion	*NAD vs. subcortical*	0.9 (0.2, 3.7)	.881	1.5 (0.3, 7.6)	.619
	other vs. subcortical	3.1 (0.7, 13.2)	.119	1.3 (0.2, 8.5)	.773
	cortical vs. subcortical	0.81 (0.4, 1.7)	.564	1.9 (0.8, 4.6)	.172
Interaction between CRT and respiratory comorbidities			**.041**		

Table 11.4 Baseline characteristics and outcomes in the experimental group by CRT result

		Fail (N: 26)	*Weak (N: 31)*	*Strong (N: 91)*	*p value*
Age mean (se)		77 (3.0)	79 (2.0)	75 (2.0)	.624
Gender (male)		15 (58%)	17 (55%)	46 (51%)	.781
Ethnicity	*NZ European*	16 (62%)	25 (81%)	70 (77%)	.670
	Maori	4 (15%)	3 (10%)	9 (10%)	
	Pacific Islander	3 (12%)	2 (6%)	8 (9%)	
	other	3 (12%)	1 (3%)	4 (4%)	
Site of lesion	*cortical*	18 (69%)	21 (68%)	63 (69%)	.593
	subcortical	7 (27%)	5 (16%)	22 (24%)	
	other	0 (0%)	2 (6%)	2 (2%)	
	NAD	1 (4%)	3 (10%)	4 (4%)	
Previous stroke history		7 (27%)	8 (26%)	29 (32%)	.769
Respiratory comorbidities		2 (8%)	7 (23%)	6 (7%)	.043
Cardiac comorbidities		21 (81%)	20 (65%)	62 (68%)	.374
Laterality of lesion	*left*	12 (46%)	10 (32%)	47 (52%)	.271
	right	13 (50%)	17 (55%)	34 (37%)	
	other	1 (4%)	4 (13%)	10 (11%)	
Domicile at admission	*public hospital*	0 (0%)	4 (13%)	3 (3%)	.164
	residential care facility	2 (8%)	2 (6%)	9 (10%)	
	home	24 (92%)	25 (81%)	79 (87%)	
Diet after 1st SLT assessment mean FOIS score (se)		2.8 (0.4)	3.3 (0.4)	4.8 (0.2)	< .001
Domicile at 3 months post stroke	*public hospital*	5 (19%)	2 (6%)	5 (5%)	.251
	residential care facility	9 (35%)	14 (45%)	41 (45%)	
	home	12 (46%)	15 (48%)	45 (49%)	
Readmission (pneumonia)		1 (4%)	2 (6%)	4 (4%)	.903
Mortality		6 (23%)	5 (16%)	9 (10%)	.071

Confirmed pneumonia		9 (35%)	10 (32%)	19 (21%)	.111
Diet at 3 months mean FOIS score (se)		6.0 (0.3)	5.6 (0.4)	6.2 (0.1)	.342
LOS in acute ward median (IQR)		7.5 (4.0, 14.0)	6.0 (4.0, 15.0)	6.0 (5.0, 10.0)	.309
Clinical practice data for patients who had instrumental assessment	*referred for instrumental assessment*	12 (46%)	8 (26%)	7 (8%)	< .001
	days between test and assessment mean (sd)	7.1 (8.4)	5.5 (5.1)	14.4 (10.4)	-
	Penetration/ Aspiration score mean (sd)	5.6 (3.1)	3.9 (2.6)	3.4 (2.7)	-

The numbers of referrals for instrumental assessment were too small for statistical analysis but descriptive analysis suggests a positive association between i) failed CRT result and silent aspiration and ii) weak CRT result and weak response to aspiration (Figure 11.5). The mean penetration/aspiration scores across CRT results suggests a trend towards more severe dysphagia leading to an increased chance of a failed CRT (fail 5.6, weak 3.9, pass 3.4).

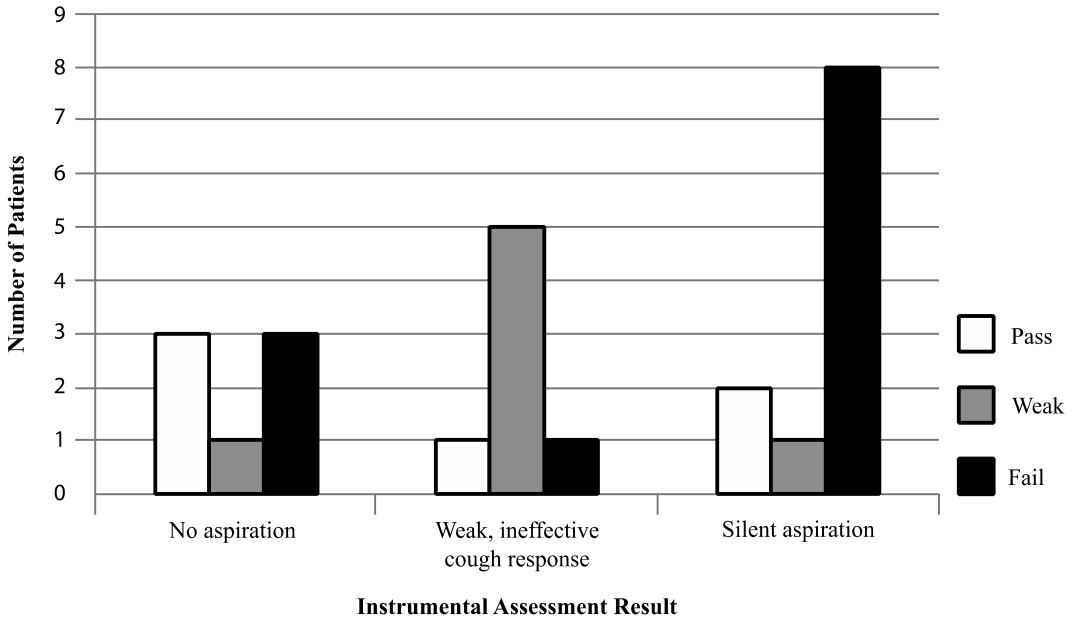


Figure 11.5 Association between CRT result and response to aspiration on instrumental assessment

11.3.3 Changes in clinical practice.

CRT results were associated with diet recommendations following initial swallowing assessment. Higher scores on the 7-point FOIS (Crary et al., 2005) were associated with better cough test results with a mean score of 2.8 for the fail group, 3.3 for the weak group and 4.8 for the pass group ($F = 13.8$, $p < .001$), mean difference and its 95% confidence interval of fail vs. pass is 2.0 (1.1, 2.9), and weak vs. pass is 1.5 (0.68, 2.3) (Table 11.4).

Overall, referral rates for instrumental assessment were 12%. The experimental group had a significantly higher proportion of patients referred for instrumental assessment than the control group (experimental 18%, control 7% with a proportion difference of 10.4% with 95% C.I. 2.9%, 17.9%, $p = .004$). The adverse responses to the CRT test were positively associated with a higher rate of referral (pass 8%, weak 26%, fail 46%, $p < .001$).

The numbers of referrals for instrumental assessment were too small for further statistical analysis but descriptive comparisons reveal a median number of days between cough test and instrumental assessment of 8.5 days in the control group compared with 3 days in the experimental group (pass 11, weak 2.5, fail 3).

There was a significant association between receiving an instrumental assessment and developing pneumonia in the control group ($X^2 = 3.98$, $p = .052$) with an odds ratio of developing pneumonia of 3.2 (95% C.I. 0.85, 12.11). Whereas in the experimental group, there was no significant association, $X^2 = 0.52$, $p = .47$ with an odds ratio of 1.4 (95% C.I. 0.52, 3.70). The odds ratios for developing pneumonia based on CRT result were more favourable for those who failed CRT: pass 3.0 (95% C.I. 0.47, 17.92), weak 1.1 (95% C.I. 0.16, 7.83) and fail 0.33 (95% C.I. 0.04, 2.31). Although there was still a surprisingly low referral rate of 46% for the fail CRT group and only 30% of those who developed pneumonia received an instrumental assessment, the odds ratio for developing pneumonia if a patient failed the cough test and had an instrumental assessment was reduced in comparison to other groups. Unlike all other groups, there was a difference in instrumental assessment referral rates in patients of the failed CRT group who did not develop pneumonia (no instrumental assessment 44%, instrumental assessment 66%) compared with those who developed pneumonia (no instrumental assessment 70%, instrumental assessment 30%) (Figure 11.6).

The timing of instrumental assessment differed depending on CRT result again suggesting changes in clinical decision-making. The five patients in the control group and two patients in the pass CRT group who received an instrumental assessment and developed pneumonia, developed this complication prior to instrumental assessment (Figure 11.6). Whereas the three patients in the failed CRT groups who received an instrumental assessment, developed their pneumonia after their instrumental assessment.

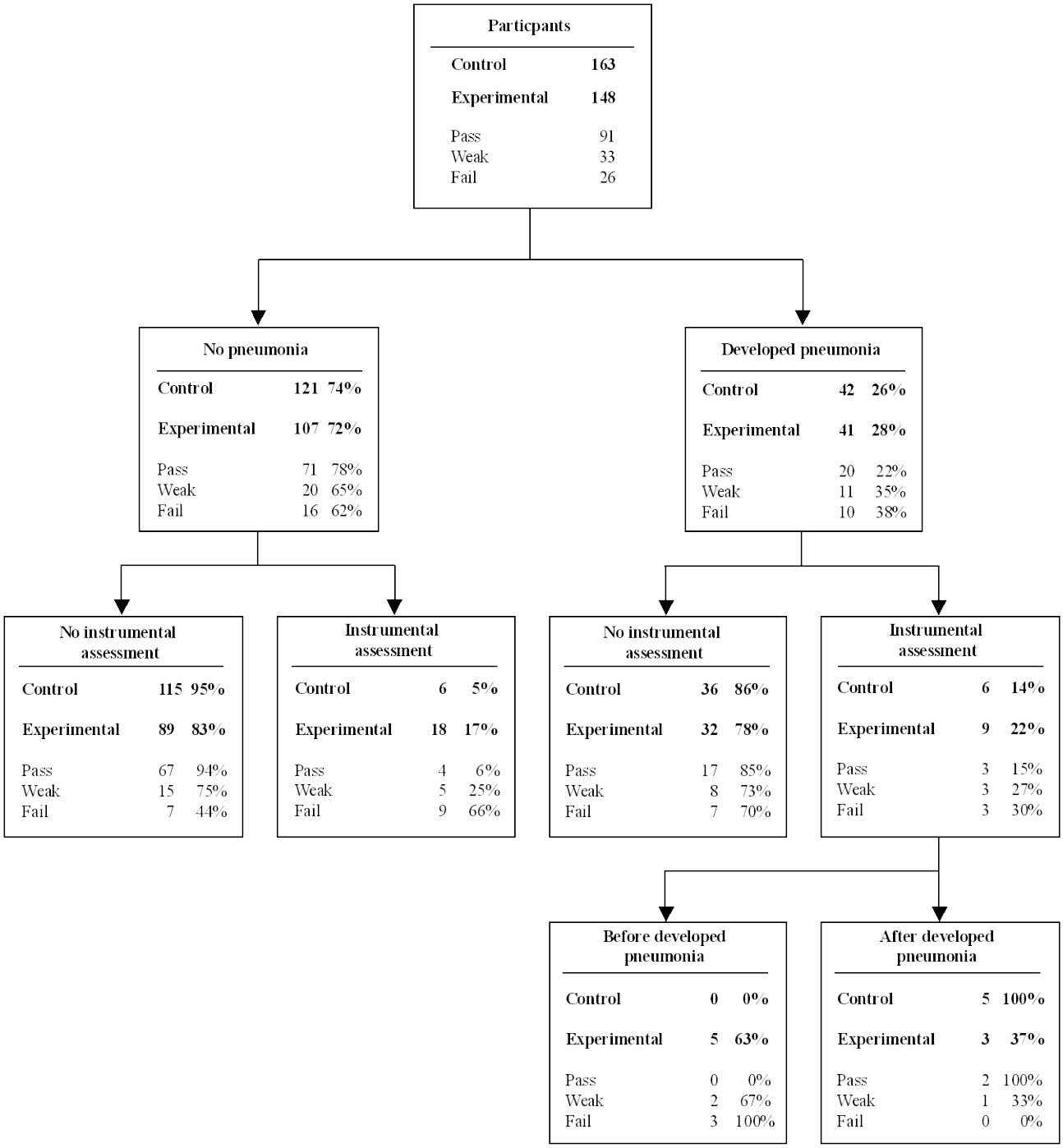


Figure 11.6 Relationship between developing pneumonia an instrumental assessment

11.3.4 Clinician survey.

Fourteen surveys were completed (8 SLTs, 2 SLT managers, 1 nursing manager, 3 staff nurses). Table 11.5 shows the tallied responses to the forced choice questions as well as extra comments provided. Four themes were derived from the qualitative comments provided by health professionals: assimilation of CRT results into decision-making, skepticism in the tool, difficulties changing habits and difficulties assimilating the new tool into decision-making (Table 11.6). Themes suggest that some SLTs perceived that they were successfully assimilating the results into their clinical decision-making. Others however, verbalised scepticism in the new tool and felt unable to justify its value to their patients without stronger evidence. Other themes suggest difficulties changing habits despite good intentions and difficulties integrating the cough test result with the rest of the CSE findings.

Table 11.5 Responses to forced choice questions

		Number of participants	*Extra comments given*
Experience of recruiting patients	*Not a problem*	1	"It was especially difficult because you didn't know the patient and you were needing to build rapport and gain confidence." "Staff reported that it frequently took greater than 20 minutes per patient." "If family not around, having to ring but if couldn't get hold of them, have to wait. This would result in doctors and nurses getting frustrated with delays if NBM"
	Occasionally time consuming or awkward	7	
	Regularly time consuming or awkward	6	
	A huge problem	0	
Did you find CRT a useful addition to CSE?	*Yes*	8	"Occasionally felt unnecessary with some stroke patients that did not need a full assessment."
	No	0	
How was it useful?	*Provided information about my patient's dysphagia*	6	"From what I understand, it is a potentially more useful (and cheaper) adjunct to the clinical swallowing evaluation than for example cervical auscultation which we funded stethoscopes in the past for." "Will be useful after initial ax. Also easier to implement if not first session. Will be useful
	Gave me confidence to	5	

	refer for instrumental assessment		if pt inconsistent, presents with complications, unsure of cough reflex."
	Gave me confidence to feed patients who passed	5	
	Gave me confidence to recommend NBM	7	
Did you find it easy to incorporate into CSE?	*Yes*	6	"I understand that some staff found this okay, others found it difficult." "Yes, as long as I had all the gear with me" "I heard reports that getting everything ready took a bit longer than usual practice."
	No	2	
Would you continue to use CRT with your patients?	*Yes*	9	"As I understand it, some of the SLTs are keen to use it a lot of the time and some are only thinking they might use it occasionally. One has expressed a preference for waiting till results are published about its value." "Yes, however it would be to supplement a bedside ax and be used after trials of food if thought needed it"
	No	0	
Does CRT have the potential to improve dysphagia management?	*Yes*	9	"When a patient shows no cough response during a bedside ax when there are other clinical signs of aspiration/penetration" "Gives me more information to base decisions on. Weak/ fail go to VFSS" "By catching silent aspirators early there's a reduced chance of aspiration, likely to do an instrumental ax. More likely to put a patient on a diet they can manage sooner e.g., thin fluids if no coughing but passed the CRT."
	No	0	

Table 11.6 Themes of implementation of CRT with representative examples of comments

Assimilation of results of CRT into clinical decision making	*Scepticism of tool and evidence base for its use*	*Difficulties changing habits*	*Difficulties with assimilation of new tool into clinical decision making*
"It provided me with more information about my patient's dysphagia"	"Didn't want to put family member through the test as too much going on"	"The doctors aren't happy with the increase in patient's being placed NBM for VFSS"	"I feel more confused now. I used to feel confident in my decision making"
"It gave me more confidence to feed patients if they passed the test"	"I'd feel more confident if there was evidence for its use. I feel like my patients are guinea pigs"	"It was a bit difficult to implement in the very first meeting with family. I can see it being easier in a successive session/ assessement. There is far too much to do in an initial assessment at times with swallow/ communication/ building rapport"	"They failed CRT but the oral trials were all fine so I've asked said thick fluids/ puree and asked the nurse to observe for signs of chest deterioration"
"I feel more confident saying NBM now I have a test to prove it"	"I'll wait until the results come out before I'll use it again"	"I found the extra equipment and supplies cumbersome"	"What do I do if they fail the cough test but everything else is fine?"
"Now I think twice when a patient doesn't cough during oral trials. It's made me less trusting of my old bedside assessment"	"I found the ethical dilemma of causing my patients discomfort for the sake of research difficult. I couldn't tell them it would be better for them."		"If they are too drowsy to eat, should I still do CRT?"
"I think this has changed the team's practice & it has made me feel more confident about my clinical decision making."	"I hardly ever see a patient who silently aspirates anyway so it seems a bit over the top"		

PART E: DISCUSSION

CHAPTER TWELVE

DISCUSSION

12.1 Validation of CRT

These are the first studies to evaluate the validity of CRT at multiple concentrations of citric acid against instrumental assessment of aspiration. CRT results were significantly associated with aspiration response on instrumental assessment with reasonable levels of sensitivity and specificity. Not surprisingly, sensitivity and specificity of the CRT for discriminating silent aspirators from overt aspirators (representing the true validity of CRT for identifying silent aspirators) was stronger than sensitivity and specificity of the CRT for identifying silent aspirators from the entire cohort of dysphagic patients (representing the capacity of CRT for accurately identifying silent aspiration during a clinical examination). There are no published data documenting sensitivity and specificity for identification of silent aspiration during CSE for comparison. However, sensitivity and specificity for identifying silent aspiration in the studies reported herein are considerably better than other individual components of current bedside examinations for identifying aspiration: jaw strength (sensitivity 26%, specificity 96%), wet voice (sensitivity 22%, specificity 96%) and soft palate structure (sensitivity 24%, specificity 93%) (McCullough et al., 2005). A 5ml water test provided 81% sensitivity but only 47% specificity while a 10ml water test provided only 37% sensitivity and 96% specificity for identifying aspiration (McCullough et al., 2005; McCullough et al., 2001). Similar levels of diagnostic accuracy were found by other researchers with low sensitivity (45%, 40% respectively) and high specificity (96%, 93% respectively) for the identification of aspiration with a water test (Mann et al., 2000; Smithard et al., 1998). Undoubtedly, sensitivity and specificity values of identifying aspiration improve when clinical observations are combined. Logemann and colleagues assessed the sensitivity and specificity of a 28-point screening tool against VFSS results. The screening test had a

sensitivity of 69% and specificity of 71% if a patient was classified unsafe on more than 8 of the 28 observations (Logemann et al., 1999). Interestingly these values for identifying aspiration from 28 observations are no greater than the values for identifying silent aspiration in Study I and II using CRT in isolation.

As well as the traditional criteria of counting coughs in CRT, cough strength was also recorded. Promising findings have been previously reported for sensitivity and specificity of objective measures of voluntary cough strength for identifying aspiration risk (Pitts et al., 2010; Smith-Hammond et al., 2009). It is not clear whether a weak cough following citric acid inhalation represents a reduced sensory receptor response to irritation or a weakened motor response. In the validity studies, when weak was classified as a fail, the sensitivity of picking up silent aspirators was improved but specificity was reduced. Overall diagnostic accuracy was greater when a weak response was not considered a failed result. Although weak cough has been shown to indicate aspiration risk, this study does not provide conclusive evidence regarding the clinical sensitivity of a weak cough response for identifying silent aspiration.

Wakasugi and colleagues found that patients who silently aspirated trace amounts were more likely to pass their CRT than patients who silently aspirated larger amounts (Wakasugi et al., 2008). Similarly in the current validity studies, sensitivity improved when trace aspirators were not classified as silent aspirators (Wakasugi et al., 2008). Trace penetration and aspiration is relatively common in healthy individuals of all ages (Allen et al., 2010) and it is also possible that FEES, where the airway to easily visualised, over-detects aspiration in comparison to VFSS. The consistent findings between these studies suggest that the presence of trace silent aspiration may not be clinically relevant.

In line with published data, more patients aspirated on fluid consistencies than solids (Daniels et al., 1998) and a number of patients silently aspirated thickened fluids but audibly

aspirated on thin fluids. These findings are clinically relevant in view of the international common use of thickened fluids as an intervention for preventing aspiration. A previous randomised controlled trial found honey thickened fluids to be the most successful intervention for preventing aspiration in 711 patients with dementia and Parkinson's disease when compared with nectar thickened fluids and chin tuck posture (Logemann et al., 2008). Further study of these mixed aspirators is required. If aspiration of thickened fluids can lead to insufficient summation to result in a cough response and small amounts of thickened fluids regularly enter the airway and are not removed, the consequences may be serious. It should be noted that in Study II, thickened fluids were tested at room temperature yet the milk used for the thin fluids was fridge-cold perhaps suggesting that stimulation of cold receptors may have led to coughing on thin fluids. Nevertheless, further investigation of the response to aspiration of thin fluids versus thickened fluids and its consequences would be valuable.

12.1.1 Failing CRT.

The CRT fail rate of these cohorts of patients with suspected dysphagia of mixed aetiology was 25% (VFSS) and 23% (FEES). This is higher than the CRT fail rate in the stroke patients in Study V (18%) and lower than the fail rate in the patients with suspected dysphagia of mixed aetiology in the Wakasugi study (30%) (Wakasugi et al., 2008). Addington and colleagues, in their study of stroke patients, found a fail rate of only 10% but their criteria was classified as "weak or absent LCR", their irritant and method of administration differed to these other studies and they do not discuss exclusion of those who were unable to achieve adequate lip seal or follow the test instructions (W. Addington, Stephens, & Gilliland, 1999, p. 1204). Of interest, if these rates are compared to the rates of silent aspiration found in our studies [21% VFSS, 36% FEES (27% with trace aspirators excluded)] and published mixed aetiology cohort studies (26%, 25%, 35% respectively)

they correlate with the CRT fail rate of the passive respiration method closely (Garon et al., 1996; C. Smith et al., 1999; Wakasugi et al., 2008). Daniels and colleagues found a similar rate of 25% in their cohort of unselected acute stroke patients (Daniels et al., 1998).

Lower concentrations of citric acid appear a better predictive measure of silent aspiration. Citric acid concentrations used in this study provide a useful working range but further testing of other concentrations may improve detection of subtle sensory deficits. Sensitivity and specificity values across different concentrations of citric acid may prove useful in different situations. Clinicians working with high risk populations may prefer concentrations that provide high sensitivity over specificity (e.g., 0.4mol/L); while clinicians using CRT as a screening tool in a low risk population may prefer to use a concentration with higher specificity (e.g., 0.8mol/L). Given the inability to identify silent aspiration by any previously mentioned criteria, CRT offers a safe, manageable tool that can be incorporated into CSE to enhance detection of silent aspiration. CRT holds promise as a swallowing screening test. CRT is safe and can be standardised, and therefore is not as susceptible to interpretative variance that plagues much of bedside clinical swallowing evaluation. The data provided in this manuscript can be used by clinicians to adapt the test to suit their clinical identification needs and allows incorporation of CRT into a dysphagia test battery.

12.1.2 Limitations.

Methodological differences between the two studies prevented pooling of data. Although the proportion of patients who passed CRT was similar between groups, a larger proportion of patients were judged as having a weak cough in the VFSS cohort (VFSS cohort 37.5%, FEES cohort 24%). This judgement was subjective. Although there was strong agreement between the two researchers at the FEES site on cough strength, differences between researchers' judgement across sites may be questioned. It is possible

that clinicians working together develop a subconscious schema for judgement over time and perhaps this differed between sites.

Despite similarities in CRT fail rates, age and aspiration rates differed across methodologies. This perhaps reflects the difference in subject selection for the clinical studies. The VFSS cohort were known to be dysphagic and were under the care of SLTs. They represented a mixture of hospitalised patients and outpatients while the FEES group were all inpatients in their first days of acute admission. Referral to VFSS requires patients to be medically stable enough to leave a ward and tolerate the radiology suite procedure while the FEES is performed at bedside perhaps allowing more unwell patients to participate. These differences in recruitment methods may have led to the differences in dysphagia severity and age. It must also be acknowledged that the cohorts were recruited from different hospitals and as well as the methodological differences, the populations may also be inherently different at the two geographically distinct sites.

As previously discussed it is also possible that FEES, where the airway to easily visualised, over-detects aspiration in comparison to VFSS. Unlike the FEES protocol, the VFSS protocol was performed by treating clinicians and was not controlled. The protocol was often truncated or terminated early. This hesitancy led to limited video-footage and perhaps patients were not challenged sufficiently leading to lower aspiration rates. The sample size for the VFSS study limited the power of some of the analysis with wide confidence intervals observed at times. Larger studies of this kind may add to the field of knowledge. The concentration of citric acid for optimal sensitivity and specificity differed between cohorts. Possible causes of this discrepancy include: cohort differences, differences in protocols and methodologies or rater reliability across sites.

Statistical limitations are worthy of discussion. Diagnostic precision is dependent on prevalence of disease and silent aspiration has a relatively low prevalence even in a selected

dysphagic population (Bender, Lange, Freitag, & Trampisch, 1997; Brenner & Gefeller, 1997). The dependence of positive predictive values and negative predictive values on disease prevalence suggests that these may be of little value in this study. Sensitivity, specificity and likelihood ratios are not influenced by prevalence and therefore may provide a more reliable measure of validity in this situation. However, caution should still be taken in comparing sensitivity and specificity values across different population groups.

The use of VFSS and FEES as a 'gold standard' assessment of silent aspiration also needs discussion. Some patients did not aspirate but perhaps if challenged more, may have aspirated (silently or audibly). An instrumental assessment does not replicate a patient's risk of aspiration throughout a meal or over the course of a day. In this study, silent aspiration was classified as at least one incident of silent aspiration observed during the assessment. Some patients silently aspirated on one occasion and audibly aspirated on another (mixed aspirators). Silent aspiration is unlikely a definable binary state. A lack of observed silent aspiration may not equate to a true gold standard for 'no silent aspiration risk.'

Finally, it is important to acknowledge some of the methodological limitations of CRT. There is inter-individual variation in cough response to irritants in the healthy population. Researchers warn that some people, without pathology, either cough excessively on very low doses of tussive agent or do not cough even on extremely high doses (Morice, 1996). Up to 10% of normal controls fail to cough on maximum doses of both citric acid and capsaicin in vital capacity breath experiments though this does not appear to occur as frequently with a 15-second tidal breathing method (Barber et al., 2003; Fujimura et al., 1996; Morice et al., 1992). This likely contributes to the calculated validity of the test and needs to be considered when using cough reflex testing diagnostically. Women have repeatedly shown lower cough reflex test thresholds than men (Becklake & Kauffmann, 1999; PV Dicpinigaitis & Rauf, 1998; Kastelik et al., 2002; Kelsall et al., 2008; Morice et al., 2000; Rostami-Hodjegan et al., 2001).

In both cohorts, females were found to pass CRT at lower thresholds than males with no females coughing for the first time at the highest threshold in the FEES cohort. In the VFSS cohort, males were also significantly more likely to fail CRT. This gender difference did not alter the final model in either cohort. However, a concentration specific to gender may prove to be a more sensitive clinical tool and deserves consideration.

12.1.3 Summary.

CRT results are significantly associated with aspiration response on instrumental assessment. Lower concentrations of citric acid provide a better predictive measure of silent aspiration. CRT can be standardised and therefore is not as susceptible to the interpretative variance that plagues much of CSE. Citric acid concentrations used in this study provide a useful working range but further testing of other concentrations may improve detection of subtle sensory deficits. Sensitivity and specificity values across different concentrations of citric acid allow clinicians to make decisions based on their clinical need.

12.2 Reliability of CRT

The CRT method in this research programme relies on assessors' ability to consistently rate cough presence and strength. It is of concern that SLTs in Study III achieved only 'fair' to 'moderate' agreement when making subjective judgements of reflexive cough without training or experience (Landis & Koch, 1977). This agreement is, nevertheless, comparable to other areas of SLT where subjective judgements are used. Inter- and intra-rater reliability in VFSS interpretation has received substantial attention (Ekberg et al., 1988; Kuhlemeier, Yates, & Palmer, 1998; Logemann, Lazarus, Keeley, Sanchez, & Rademaker, 2000; McCullough et al., 2001; Scott et al., 1998). Rosenbek and colleagues found high agreement for experienced judges using the PAS (ICC .96) (Rosenbek et al.,

1996) but many other researchers have described lower levels of agreement. Ekberg and colleagues report large variation across VFSS measures with a Kappa value of .57 for presence of penetration and Kuhlemeier and colleagues found only 30% agreement for abnormal ratings and 78% agreement for normal ratings of VFSS analysis (Ekberg et al., 1988; Kuhlemeier et al., 1998). Similar variations in agreement levels have been seen in perceptual voice assessment, where agreement can range from high to low depending on the measure, the type of rating (i.e., binary vs. rating scale) and the training/ experience of the rater (Kreiman, Gerratt, Kempster, Erman, & Berke, 1993; Oates, 2009; Webb et al., 2004).

12.2.1 Training effect.

The impact of training on reflexive cough judgement is more encouraging. Considerably stronger agreement was found in Study IV when specific cough physiology and cough judgement training was provided. Despite higher agreement levels with training, cough presence was still more consistently judged than cough strength with qualitative comments strongly reflecting continued uncertainty regarding the subjective nature of the strength rating. In Study III, clinicians appeared to lack a clear understanding of the definition of a cough and it is possible that internationally SLTs do not consistently receive training in cough physiology at an undergraduate level. Similar positive outcomes from education and training have been achieved in other areas of SLT such as voice (Oates, 2009) and VFSS analysis (Logemann et al., 2000). Logemann and colleagues studied the effectiveness of four hours of training on the VFSS interpretation of 90 SLTs (Logemann et al., 2000). They found a significant reduction in incorrect responses (using an expert researcher as the gold standard) with the training. There are therefore potential benefits of in-house training for strengthening clinician agreement regarding subjective cough judgements.

Comparable to other recent data from our laboratory, SLTs with CRT experience did not have stronger agreement than those with no CRT experience in Study III (Teng & Huckabee, 2012). Yet, SLTs with CRT experience and specific cough judgement training had more agreement than those with cough physiology training alone. Experience would be expected to lead to improved agreement. The theories of experiential learning suggest that advanced cognitive processing comes from repeated experience, reflection, generalization and application over time (Kolb & Fry, 1975). It must be acknowledged that the cohort with CRT experience also worked as a clinical team. Previously research with high levels of cough judgement agreement have been found in research teams where perhaps a 'team-schema' for rating occurs over time and through constant peer review (Daniels et al., 1998; McCullough et al., 2005; Rosenbek et al., 2004). The two researchers in Study II who had spent considerable amounts of time developing study protocols and criterion also achieved high levels of agreement on cough strength judgement. Scott and colleagues report similar improvements in VFSS analysis agreement when participants were able to discuss videos prior to independently rating them (Scott et al., 1998). This improvement in agreement with a combination of specific training, experiential learning and peer review holds promise for the use of cough judgement in clinical practice. With more directed training, all clinicians may reach greater agreement in reflexive cough judgement.

12.2.2 Years of dysphagia management experience.

An educated yet arbitrary split of those with under and over five years of experience in working with patients with dysphagia was made in order to investigate the effect of experience on agreement. Cough presence judgement was stronger for those with under five years experience compared with those with over five years. Although changes in undergraduate training of cough physiology over time may account for this difference, it

must be noted that the CRT experienced cohort were less experienced than other site groups and this may be a confounding variable impacting on these statistics. The theory of experiential learning would suggest that those with more years of experience would be more reliable in their judgements and this has been found in the VFSS reliability literature (Logemann et al., 2000). Conversely, if cough judgement is not a routine component of a SLT's CSE then experience in dysphagia management may not necessarily equate to any experience in judging cough. Finally, the majority of participants in this study were relatively experienced and further studies with less experienced participants and perhaps SLT students would allow for stronger conclusions regarding the impact of experience on cough judgements. Comparing SLT agreement with the agreement of medical professionals with specialist skills in cough physiology and assessment such as respiratory physicians and respiratory physiotherapists would add value.

12.2.3 Limitations.

There were a number of limitations to the pilot study, Study III. Although experience in CRT was documented, information regarding the overall clinical experience of the participants was not collected. The impact of clinical dysphagia experience on intra- and inter-rater reliability cannot therefore be determined. Videos were consecutively obtained and were not systematically selected. In allowing participants to talk after the first viewing, bias could have been added but there is clearly little impact of this, as participants did not markedly change their ratings across viewings. It could be argued that the intra-rater reliability is more a representation of the SLTs' confidence in their decision-making than a measure of intra-rater reliability. With only ten videos and a 15-minute break between viewings, even with an altered order of presentation, SLTs may have recalled the rating they had made previously for each clip. The higher agreement values for intra-rater reliability

therefore may demonstrate that the raters were not particularly indecisive and remained confident in their original decisions during the first viewing when they rated the second viewing videos.

A number of the limitations of Study III, were improved upon in Study IV. The sample size had adequate power to allow more confident interpretation of kappa coefficient scores across experience subgroups. Data on clinical experience in dysphagia were collected allowing discussion of the impact of experience levels on rater agreement. The Kappa statistic has some methodological issues that are worthy of discussion. Kappa coefficient is influenced by prevalence of the disease. This was controlled through a balanced selection of cough samples including the addition of two videos thought to represent normal elderly coughs. Different videos were used in the two studies and the impact of this on prevalence and comparability must be considered. The number of categories available to raters also influences kappa coefficients. The more categories available, the larger the likelihood for disagreement, resulting in lower kappa coefficients. Guarded interpretation is needed when comparing kappa values from studies with differing category numbers. To allow comparison between studies and within studies, this statistical limitation was controlled through the use of both two-category and three-category analysis.

Shoukri warns against increasing raters to maximise power in agreement studies and states that having more than three raters makes little difference to power (Shoukri, 2010). Increasing the number of subjects, in this case, videotaped examples of coughs, is considered to be more appropriate. In fact, in Study II, the FEES validation study, inter-rater reliability was ‘almost perfect’ for both cough presence (CRT threshold) and cough strength for the two researchers across 100 videos. The use of professional development events for recruitment in the reliability studies necessitated the researchers to minimize the amount of time required for participation and therefore increasing the number of videos was not

feasible. This first statistical approach, however, appears appropriate where reliability of a specific test is in question. Where overall group agreement is of interest, numbers of raters becomes more relevant. Limiting the number of raters to two or three would limit the opportunity to consider the impact of experience levels and training on agreement or the generalisability of the results.

In keeping with the C2 scoring method, video clips showed only 15 seconds of a patient's response to tussive stimuli. Agreement in judgements may have been better if longer observation periods were given. In clinical practice, consistency of response would be determined over three trials before making a final judgement. It is important to acknowledge the potential auditory barrier in the use of cough reflex testing to judge cough. The noise of the nebuliser was mentioned in the qualitative data as affecting the ability to hear the cough clearly.

The patient's physical appearance may adversely affect judgement of strength. One video presented a frail gentleman lying in bed. He was judged by the researchers to have a strong, prompt cough but raters showed significant variability in their judgements between strong and weak. At a perceptual level, decision-making of sensory information is thought to involve multi-sensory perception and attention. This can be complimentary in that additional sensory information (e.g., visual) may aid another ambiguous input (e.g., auditory) (Alais, Newell, & Mamassian, 2010). However, one sensory input can also bias another and visual modalities are thought to be more dominant than other inputs (Alais et al., 2010). This may explain the possible visual response bias of the sick elderly gentleman. In another video, a young man produces large amounts of extraneous cough-like movements of his upper body, yet there is no audible cough. Responses again were mixed between weak and absent cough suggesting a possible visual bias in decision-making at the perceptual level or perhaps more cognitively driven. A recent study in our laboratory investigating the

influence of visual versus auditory cues on cough judgement in 111 SLTs did not find a significant difference in cough presence agreement when SLTs had access to auditory cues ($\kappa = 0.75$) only or auditory and visual cues ($\kappa = 0.76$) (Teng & Huckabee, 2012). However, as with the present studies, SLTs regularly commented on using visual information including perceived distress and body movements when making their judgements.

Ratings were independent in the present studies but the influence of professional bias is unknown. Weak cough was poorly agreed upon and less frequently chosen. Clinician caseload and experience could impact on judgements. Qualitative comments suggest uncertainty about 'weak' and an awareness in some clinicians that they were accepting less than adequate coughs as strong due to their environmental bias. A clinician's own 'internal standards' and how this influences clinical judgement has been extensively researched in the area of the perceptual evaluation of voice (Gerratt, Krieman, Antonanzas-Barroso, & Berke, 1993; Oates, 2009). Clinicians' experience and training could likewise influence cough strength judgement. A clinician who works with a neurologically impaired and/or elderly population is likely to perceive strength of cough differently to a clinician working in an outpatient ENT clinic. Bias influences kappa coefficient with larger levels of bias leading to strong kappa scores. It must be acknowledged that strong agreement in ratings only provides information about inter-rater reliability and does not provide any information about the validity of these ratings. It is not possible to make conclusions regarding accuracy of judgements in these studies.

12.2.4 Summary.

Untrained SLTs were only fair to moderately reliable in subjectively judging cough. However, when SLTs were given a two-hour training session on cough physiology and cough judgement, substantial agreement was achieved for both cough presence and cough

strength especially in those with previous clinical CRT experience. Objective cough strength measures were not used in this study so no conclusion can be made about the accuracy of SLTs judgements, only their agreement. A comparison of an objective reflexive cough measure (such as airflow measures) versus subjective judgement of cough strength would add further to this area of research. Research has shown both abnormal voluntary cough strength and reduced cough sensitivity as risk factors for pneumonia (W. Addington, Stephens, & Gilliland, 1999; Smith-Hammond et al., 2009). A reliable cough reflex test (pass/ fail) with a subjective strength rating (weak/ strong) may prove a beneficial additional tool to the clinical swallowing evaluation. Clinically, there are difficulties in assessing voluntary cough in patients after stroke secondary to barriers of impaired cognition, communication and apraxia (W. Addington & Widdecombe, 2009; Stephens et al., 2003). A judgement of reflexive cough strength may certainly be more useful for identifying those at risk of being unable to clear aspirated material than a voluntary cough judgement (Magni et al., 2011). Undergraduate programmes and in-house training should ensure SLTs have a good understanding of cough physiology and have the opportunity to develop confidence in subjective weak cough judgement in order to guarantee that this component of the CSE is reliable and clinically relevant.

12.3 Clinical Utility of CRT

Study V assessed the utility of CRT for changing functional outcomes in patients with dysphagia following stroke. The CRT used a stable tussive agent of controlled doseage and a passive facemask method appropriate for a neurologically impaired population. The test involved a citric acid evoked cough test, a suppressed cough test that was hypothesised to represent a true reflex cough and a subjective test of cough strength (R. Eccles, 2009; Hegland et al., 2012). Based on prior research (W. Addington, Stephens, & Gilliland, 1999;

Wakasugi et al., 2008), we hypothesised that inclusion of CRT in a CSE protocol would provide clinicians with critical information that would subsequently alter management plans sufficiently to reduce the end outcome of pneumonia. Our data suggest that clinicians did integrate information into diet selection as well as frequency and timing of referrals for instrumental assessment. However, incorporation of the test results into multidisciplinary practice was insufficient to change health outcomes.

The development of pneumonia is multi-factorial (Langmore et al., 1998). A single change in the course of a patient's assessment may not to be powerful enough to alter this primary endpoint unless that change strictly controls a host of consequent management practices. Addington and colleagues did find a difference in pneumonia rates between their hospital with CRT and their 'control' hospital without CRT, but there is significant bias introduced to their study. By using the mouthpiece method of delivery, they likely limited participation to patients who were able to form sufficient lip seal, control respiration and follow instructions, perhaps excluding those most at risk of pneumonia from the experimental group. In using a sister hospital for comparison, control is compromised for inclusion criteria in the study sample in terms of both geographical differences between hospitals and clinical practice differences.

Despite the concerning gaps in CSE in the acute inpatient setting, studies have successfully documented reduced pneumonia rates through SLT involvement. In 2010, Matrix Evidence published a report stating the annual cost benefit of SLT for post-stroke dysphagia exceeds the annual cost of therapy by £13.3 million in the UK (Marsh, Bertranou, Suominen, & Venkatachalam, 2010). They calculated that every £1 invested in SLT generates savings of £2.3 in healthcare costs through avoided chest infections (Marsh et al., 2010). The Matrix Evidence report was based on the results of a published randomised controlled trial (Carnaby, Hankey, & Pizzi, 2006). This trial compared physician-only care to low intensity SLT and high

intensity SLT in 306 patients post stroke and found improved outcomes for patients who received more SLT input. The probability of developing pneumonia with SLT involvement was 25% compared with 47% without SLT and high intensity therapy was significantly associated with return to normal diet by 6 months (Carnaby et al., 2006). The term "SLT intervention" was used broadly and was not standardised or controlled. Low intensity input was described as three times weekly compensatory strategy advice and diet modification review; while high intensity input was described as daily direct swallowing exercises. The broadness of these definitions makes it difficult to extrapolate the causal factors for change in outcomes. It is unclear from this paper how this difficult blinding of staff from the daily interventions could be successfully accomplished. What it does suggest is that frequent review and reassessment of patients offers the best chance of detecting changes or deterioration.

Other studies have documented reduced pneumonia rates by the simple addition of dysphagia assessment protocols (Hinchley et al., 2005) and clinical dysphagia pathways (Odderson, Keaton, & McKenna, 1995). In both of these studies, a variety of assessment tasks were introduced and subsequent clinical decisions were strictly controlled. Hinchley and colleagues collected data at 15 institutions and found reduced pneumonia rates in patients who received formal nurse-led swallowing assessments (formal swallowing assessment 2.4% vs. no formal swallowing assessment 5.4%, $p = .002$) (Hinchley et al., 2005). The assessments included clear actions depending on the response to each task in the assessment. The lack of a control group and the variations between assessment protocols used across institutions perhaps limits the power of these results.

Odderson and colleagues introduced an initial swallowing assessment in their hospital and none of their 124 patients developed pneumonia compared to the stroke pneumonia rate prior to its introduction of 6.7% (Odderson et al., 1995). Again the assessment covered a range of criteria (following commands, voice, cough, water test,

secretion management) and was accompanied by a strict clinical decision pathway. A registered nurse or SLT completed the assessment. The study was small and pre-pathway data were not collected other than hospital statistics on pneumonia rates making inferences about homogeneity of groups difficult.

Dictating clinical behaviour due to one variable may be short sighted and may not represent the whole clinical picture. Pneumonia is an inherently complex outcome to manipulate secondary to its multifactorial causes. Studies with a more objective diagnostic assessment of pneumonia may allow for the detection of aspiration pneumonia and exclusion of other types of pneumonia from analysis. In contrast, studies controlling for other causes of aspiration pneumonia such as poor oral hygiene and poor dentition may also lead to more positive results. Perhaps developing protocols that account for many variables, like these successful examples, may be more effective in reducing secondary complications (Hinchley et al., 2005; Odderson et al., 1995). Further investigation into the integration of information in multi-disciplinary decision-making and clinical pathways is warranted to assess the true benefits of cough testing on patient outcome.

12.3.1 Changing clinical practice.

The complexity of changing clinical practice at the individual or group level is well documented (M. Eccles, Grimshaw, Walker, Johnston, & Pitts, 2005; Grol & Grimshaw, 2003). SLTs in this study were expected to incorporate a new tool, the CRT, into their current bedside swallowing assessment protocol. Although some significant changes in clinical decision-making were reported, qualitative remarks made by clinicians after the recruitment period suggest difficulties in assimilating the new tool into service delivery. In this study, it was acknowledged that development of pneumonia is dependent on a number of factors and individual clinicians were permitted to integrate this new information from

the cough test into their existing decision making construct. However, in doing so, it allowed for significantly greater degrees of freedom in leading to final outcomes: that of clinician skill and choice. This may account for the lack of difference in outcomes between our cohorts.

Applying research evidence into practice improves patient outcomes; yet, the challenges of changing clinical practice have been deliberated by many healthcare professions for a number of decades (Benner, Hughes, & Sutphen, 2008; Dopson, Fitzgerald, Ferlie, Gabbay, & Locock, 2010; Grol, 1997). In 1997, there were 15 published systematic reviews on changing clinical practice and/or implementing clinical guidelines and new research (Grol, 1997). In a systematic review, Grilli and Lomas found the compliance rate of clinical recommendations in clinical guidelines was only 54.5% (Grilli & Lomas, 1994) emphasising that publication of guidelines and research is not sufficient to change practice (Freemantle et al., 2000). The strength of evidence for a new practice is clearly important yet it has not been proven sufficient to lead to clinical change (Dopson et al., 2010).

Implementation of research and evidence based guidelines have been described as haphazard in the past and without scientific approach (M. Eccles et al., 2005). A great range of implementation approaches has been recounted, perhaps reflecting the different theories underpinning different professional groups. The most common implementation approaches reported in the literature are: education, audit, email reminders, development of new roles with designated novel tasks, media campaigns, institution-led quality initiatives and financial interventions (Grol & Grimshaw, 2003). Dopson and colleagues describe the success in adoption of new ideas as the interaction between the innovation (the complexity of the new tool, the strength of evidence behind it), the adopter (personal attitudes, skills) and the environment (the organisational support) (Dopson et al., 2010). No one

implementation approach has been proven superior to another and different approaches work in different settings and with different professionals (Grol, 1997). Many experts conclude that a multi-facetted approach is the most likely to succeed (Feder, Eccles, Grol, Griffiths, & Grimshaw, 1999; Grol & Grimshaw, 2003).

12.3.2 Barriers to changing clinical practice.

Barriers to changing clinical practice have been frequently reported as related to either the organisational context (financial or organizational constraints, influence of opinion leaders) or the knowledge and attitudes of the health professionals (clinical uncertainty, self confidence, information overload, habit) (Grol & Grimshaw, 2003). McCaughan and colleagues examined nurses' perception of barriers to implementing new research into practice (McCaughan, Thompson, Cullum, Sheldon, & Thompson, 2002). They interviewed 108 acute hospital nurses and found nurses lacked confidence in interpreting published research findings and in their own skills to use new information. They felt unsupported by their organisation to change practice and were sceptical of the research findings or their applicability in clinical practice (McCaughan et al., 2002). Green and Seifert argue that most implementation approaches focus on the dissemination and translation of information and pay little attention to the adoption of new procedures that incorporate the new information into practice (L. Green & Siefert, 2005). It has been demonstrated that overcoming habits or well-established practices to integrate new knowledge is hugely challenging (Anderson, 1982).

Organisational implementation barriers were not reported in Study V but personal barriers were evident. Clinicians reported being confused and lacking confidence in their decision-making. The fact that only 50% of patients who failed CRT received an instrumental assessment and only 46% of them were placed nil-by-mouth indicates distrust

in the new tool and lack of incorporation of CRT results in clinical decisions. There were requests for more evidence and reports of hesitancy to place patients nil-by-mouth by SLTs and doctors. SLTs had received training in the theory of CRT and the current literature. They had a practical session on using the equipment and carrying out a CRT protocol and clinicians were encouraged to provide each other with peer support. The researchers were available via email and phone and were on-site regularly to provide ongoing guidance on implementation of cough test results into clinical practice. Yet, when the clinician survey was given out after recruitment was completed and the clinicians had been using CRT for nine months, some of the comments suggested faulty theoretical knowledge and clinical reasoning. For example, one clinician stated that she doesn't see many patients with silent aspiration; others wanted to use CRT at their own discretion. A number of clinicians, when faced with a failed CRT but no coughing on oral trials, chose to trust the oral trials and discount CRT results. Many of these remarks suggest that clinicians still did not understand or did not agree with the concerning lack of indicators of silent aspiration at bedside and the unique addition that CRT could make. Alternatively, clinicians may have been reluctant to be led by the CRT result as it suggested faults in their current practice that they were uncomfortable to consider.

12.3.3 Clinical decision-making.

The intricacy of integrating new information into a clinician's imbedded practice may be a genuine barrier to changing clinical practice in response to a new tool such as CRT. Clinical decision-making is "the ability to sift and synthesize information, make decisions and appropriately implement these decisions in the clinical environment" (O'Reilly, 1993, p. 2). This is a complex process involving observation skills, solid clinical knowledge, previous experience, problem-solving, creative thinking skills and self-belief

(O'Reilly, 1993). Hardy and Smith describe clinical decision-making as the process of making informed judgements by following the overt and covert 'clues' in the case history, patient report and clinical presentation (Hardy & Smith, 2008). Knowledge and experience are critical to this deductive cognitive skill (Benner et al., 2008).

Green and Seifert describe the cognitive process by which a clinician i) constructs the new knowledge as memory ii) translates this into procedural rules then finally, iii) rehearses the new procedural rules until they become automatic and synthesized into practice (L. Green & Siefert, 2005). It is not surprising that this intuitive synthesis of information becomes more skilful and swift with experience and that absolute integration of a new tool takes time (L. Green & Siefert, 2005; O'Reilly, 1993). As a cognitive psychologist, Anderson states, it takes "at least 100 hours of learning and practice to acquire any significant cognitive skill to a reasonable degree of proficiency"(Anderson, 1982, p. 369). The complexity of clinical decision-making lies in the absence of clear-cut rules. This need for complex interpretation puts a heavy burden on working memory and requires repetition over time to become efficient (Anderson, 1982). The difference between novice and expert is that the expert no longer needs to rely on rules and logical thought and can see a clinical presentation as a complex whole (Benner et al., 2008). This is often referred to as clinical intuition (Benner et al., 2008).

12.3.3.1 Challenging old habits.

The clinician survey brought up a strong theme of difficulties changing habits. All SLTs reported CRT useful and 75% reported that it was easy to incorporate into their practice; yet, many complained about the additional equipment and additional time taken with the test. The challenge of changing their assessment routine was evident in the survey and during ward observations. Regularly clinicians verbalised a desire to trust their clinical

intuition and oral trials observations; “I know he failed CRT but he did really well on the oral trials, he didn’t cough” rather than trust that CRT was adding more information to the clinical picture than they’d previously had available. This again perhaps suggests a feeling of personal failure if they were to change their usual practice rather than an openness to change and improve their assessment tools.

12.3.3.2 Developing a new schema.

Clinical decision-making is complex and with any new test comes new ‘clues’ for the clinician to decipher. Development of a new schema of patient responses, which incorporates CRT responses, takes time. Qualitative remarks from the SLTs involved in the clinical trial suggest some embraced the new knowledge and incorporated it well into their swallowing assessment ‘schema.’ Some were resistant to change or sceptical of novel approaches. While others, despite good intentions, struggled to reach the final cognitive process of a new automatic procedural schema with cough reflex testing integrated. It could be predicted that clinicians during the recruitment period were still relying on procedural rules and logic (at a novice level) rather than being able to fully incorporate CRT as a complex whole (at an expert level). It is highly probable that one limitation in this study was that the clinicians were expected to embed a new tool into their clinical decision-making without a sufficient period of adaption. Although the clinicians performed the CRT during the trial period, their skills in interpreting the results were perhaps not optimal. Further research in this area would be beneficial. Future directions may include re-evaluation of the same clinicians after a longer period of assimilation and the impact on functional outcomes with strict clinical pathways in place.

12.3.4 Association between CRT result and other clinical factors.

Reduced cough sensitivity and silent aspiration have been associated with poor functional outcomes (W. Addington et al., 2005; Pikus et al., 2003). Eighteen percent of patients in the experimental group failed CRT. This is similar to the proportion of silent aspirators reported in previous unselected acute stroke cohorts (25%) (Daniels et al., 1998). However, contrary to published data on cough sensitivity and silent aspiration, failing CRT was not significantly associated with poorer outcomes (initial diet recommendations, pneumonia and mortality) although trends for pneumonia and mortality were noted (Schmidt et al., 1994; Teasell et al., 1996). In Study V, CRT results were not significantly associated with age, gender, ethnicity, stroke history, cardiac comorbidities, stroke type or independence on admission. Conversely, in Study II, patients who failed or had a weak CRT were significantly older than those who passed CRT. Both neurological origin of dysphagia, respiratory comorbidities and being male (in Study I) led to increased odds of failing CRT in patients who silently aspirated. This perhaps reiterates the difficulty in predicting those most at risk of diminished cough sensitivity or silent aspiration at bedside. There may be clear clinical predictors for dysphagia in a patient's clinical history but a clear predictor of silent aspiration has proven more difficult to calculate.

12.3.5 Weak cough.

Weak voluntary cough has been associated with aspiration and pneumonia (Pitts et al., 2010; Smith-Hammond et al., 2009). The strength of a reflexive cough response to citric acid may provide vital information about the extent to which the sensory receptors responded to the irritant (sensory impairment) or may indicate weakened inspiratory and/or expiratory muscles (motor impairment). In the validity studies, weak cough was

significantly associated with silent aspiration but overall classifying weak cough as a failed CRT did not optimise sensitivity and specificity values. Study V, however, shows a difference in functional outcome for those in the weak cough group compared with both the pass group and fail group. As well as significantly higher respiratory comorbidities, patients in the weak group had a trend towards higher mortality and higher pneumonia rates than those in the pass group. Interestingly, clinicians treated patients with a weak cough result differently. They had a higher rate of instrumental assessment than the pass group, lower FOIS diet recommendations on admission and the fastest referral rate to instrumental assessment of all groups. Patients with respiratory comorbidities in the experimental group had significantly lower pneumonia rates than those in the control group. This proposes that clinicians treat patients with weak reflexive cough differently and that CRT may be a useful tool in identifying those with compromised ability to clear aspiration. It also implies that patients with weak reflexive coughs, when managed more cautiously, may have more positive outcomes. Respiratory comorbidities were significantly associated with weak cough, giving strength to the reliability of weak cough judgements by SLTs. However, the proportion of patients rated as weak differed greatly across research sites and although this may be due to geographical differences in patients' clinical presentation, it must be acknowledged that this judgement was subjective. Clinical protocols that attend to weak reflexive cough independently of presence/ absence of reflexive cough may prove more clinically useful. A clinician should first attend to risk of silent aspiration by counting coughs then judge risk of weakened ability to clear aspirated material by judging cough strength. This would provide a more considered assessment of pneumonia risk and allow informed early dietary recommendations to be made.

12.3.6 Clinician behaviours.

The data show that pneumonia rates for those who passed CRT were as poor as for those in the control group. This may suggest an over-reliance on the result of the CRT in clinical decision-making in patients who passed CRT, perhaps overlooking other assessment findings. The CRT is a simple test of airway sensitivity and does not answer clinical questions regarding dysphagia severity. For patients in the control group and patients in the experimental group who passed the CRT, clinicians were using pneumonia as a clinical indicator of aspiration and only referring for diagnostic assessment when pneumonia developed. In view of the increased risk of mortality and increased LOS associated with the development of pneumonia after stroke, this reactive rather than proactive practice in clinical reasoning is of serious concern (Aslanyan, Weir, Diener, Kaste, & Lees, 2004). In the failed cough test group, although only half of patients were referred for instrumental assessment, different clinical decisions were being made. Instrumental assessment occurred earlier and without waiting for the development of pneumonia and for those referred for instrumental assessment, clinical outcomes were more positive. Very little has been published on the impact of instrumental assessment on pneumonia rates and further research into the effects of early instrumental assessment referral could support clinical protocol development.

12.3.7 Limitations.

There are a number of limitations to this clinical trial. The experimental group and control group did not differ in age, LOS, comorbidities, stroke type or site or initial diet recommendation. This strongly suggests homogeneity between groups but the addition of an accepted stroke severity or handicap measure would have added to this comparison and to the overall interpretation of clinical outcomes. The primary and secondary outcome

measures were gathered by telephone and chart review, therefore running a risk of recall and surveillance bias. Information was gathered from GPs, residential care staff, patients, families and clinical records in an attempt to reduce this risk. Aspiration pneumonia was not distinguished from pneumonias of other causes and a more objective diagnostic assessment of aspiration pneumonia may have led to different results. However, this more complex testing is not commonplace in stroke or dysphagia studies.

The use of more controlled management protocols, including a validated CSE and a strict clinical pathway, may have led to a clearer reduction in pneumonia rates. All clinicians received the same training, followed the same CRT protocol and were given the same guidelines for integration of the CRT results into management decisions but followed local policies and procedures. Reliability of clinician assessment, interpretation and action is uncertain and this is emphasised in some of the responses provided in the survey.

12.3.8 Summary.

There is great interest in the development of a bedside test for 'silent aspiration' in the field of acute dysphagia management. In this study, knowledge of cough response did not decrease pneumonia rates, suggesting that inclusion of CRT alone is not sufficient to change clinical outcomes. Although the findings that negative CRT outcomes were associated with higher risk of mortality and pneumonia did not reach statistical significance, they very likely are clinically significant. Management was not controlled and integration of CRT into a clinical pathway that also controls for the other known predictors of pneumonia and specifies the clinical decisions of clinicians may prove more successful. CRT is a test solely of airway sensitivity and may be useful as a screening tool or integrated into a comprehensive, validated CSE. The positive validation results in Study I and II suggests that with the addition of CRT, the diagnostic accuracy of the CSE for detecting silent aspiration would

improve. Further research into the clinical utility of this clinical tool would add value to the clinical field. Consistent implementation of CRT results into clinical decision-making was not investigated in this study and may have influenced subsequent patient outcomes. Research looking at controlled integration of information into multidisciplinary clinical decision-making and clinical pathways, is warranted.

PART F: THE NEW ZEALAND CONTEXT

CHAPTER THIRTEEN

STUDY VI. CLINICAL OUTCOMES FOR PATIENTS WITH DYSPHAGIA AFTER STROKE IN NEW ZEALAND: A DESCRIPTIVE STUDY [12]

13.1 Research Question

Through the collection of data for Study V, an incidental sample of patients with dysphagia after stroke in New Zealand was obtained. The clinical outcomes of patients with dysphagia after stroke in New Zealand have not been previously reported or benchmarked against international standards. No specific hypotheses were proposed or evaluated in this study but the questions remain unanswered: what are the clinical characteristics and clinical outcomes for patients with dysphagia after stroke in New Zealand and how do they compare internationally? Defining New Zealand-specific characteristics and outcomes will guide nationally based research and health care initiatives that will in turn improve clinical outcomes and streamline health costs. The aim of this descriptive study was to define the clinical characteristics and clinical outcomes for patients with dysphagia after stroke in New Zealand with the purpose of comparing these data with current international and national studies.

[12] *Miles, A., McLauchlan, H. & Huckabee, ML. (under revision) Clinical outcomes for patients with dysphagia after stroke in New Zealand: original article. Speech, Language & Hearing. Revision submitted 21st March 2013.*

13.2 Methodology

13.2.1 Patient selection.

Three hundred and eleven acute stroke patients (165 females, 146 males) consecutively referred to speech-language therapy for swallowing assessment were recruited from four urban hospitals. Patients were referred following a failed dysphagia screen and the number of stroke patients per site who were not referred to SLT is unknown. All participants gave informed consent independently or consent was gained by proxy. Due to the purpose of the concurrent clinical trial, patients were excluded if palliative swallowing advice was requested rather than active treatment on admission.

13.2.2 Study design.

This study received appropriate national ethics approval (NTY/09/11/113) as a randomised control trial looking at the clinical utility of cough reflex testing after stroke. Detailed results of this experimental trial are reported in Study V. This chapter will focus strictly on identifying the characteristics and outcomes associated with dysphagia secondary to stroke in New Zealand; the full cohort of participants (irrespective of their randomisation) will be discussed. Details of patient information and outcomes collected are described in Study V, Section 11.2. Costs associated with stroke admissions in 2011 were also requested from each DHB. DHBs were asked to provide three pieces of financial information: i) cost of 24-hour stay on a stroke ward, ii) average cost of a stroke admission and iii) average cost of a stroke admission if pneumonia also present.

13.2.3 Data analysis.

Statistical analysis was completed using SAS version 9.3 (SAS, Cary, NC, USA) and SPSS version 20 (SPSS, Chicago, IL, USA). Two-sample t-test (t) was used to compare

the median length of stay (LOS) between those who developed pneumonia and those who did not. ANOVA was used to evaluate age across ethnicities. Chi square test was used to assess the associations between binary and categorical outcomes. Multiple logistic regressions were applied to evaluate the effect of confounding variables on pneumonia and mortality (gender, hospital site, ACE inhibitors, cardiac comorbidities, previous stroke history, respiratory comorbidities, instrument assessment and lesion locations). AIC was used as the selection criteria. Firstly the full model with all confounding factors was fit, and a backward selection was used to select the main effect model.

The results from the current study are compared to the National Acute Stroke Service Audit 2009 allowing a comparison of the outcomes of patients with dysphagia with local data (Stroke Foundation of New Zealand, 2010). This audit was published by Stroke Foundation New Zealand and comprised of an organisational survey of all 21 New Zealand District Health Boards and a clinical audit at 20 New Zealand District Health Boards. As part of the clinical audit, the records of 40 consecutive patients admitted with a diagnosis of stroke from each District Health Board were reviewed. The report describes the clinical management and characteristics and outcomes for 832 patients during their acute hospitalisation. The results were then compared with international data from published stroke studies.

13.3 Results

13.3.1 Patient characteristics.

Fifty-three percent of patients were female. The patients' ages ranged from 22-102 years (mean of 78 years, SD 13.5). The majority of the patients were New Zealand European (NZE) 66%, followed by Pacific Island 10%, New Zealand Maori (NZM) 9%, Asian 5%, European 8%, and other 3% (of whom 2 were South African, 3 Russian, 2

Canadian and 2 Australian). All patients presented clinically with an acute stroke. Initial CT scans classified lesions as follows: cortical 68%, subcortical 15%, brainstem 3%, cerebellar 4%, multilevel 3%, small vessel disease 2%; no new abnormalities detected on CT scan 6%. The pre-morbid health conditions and risk factors for participants included respiratory comorbidities 13%, diabetes 15% and previous stroke 29%. ACE inhibitor prescription rates were 35%. At the time of admission, 86% of patients lived at home and 14% lived in residential care.

13.3.2 Ethnicity.

Gender, previous stroke history, cardiac comorbidities, respiratory comorbidities, diabetes, site of lesion, pneumonia, mortality, independence at 3 months and CRT result were not significantly associated with ethnicity (Table 13.1). Hospital site was significantly associated with ethnicity with 80% of patients identifying as New Zealand European at Hospital B compared with only 50% at Hospital C ($X^2 = 44.90$, $p < .001$). Age was also significantly associated with ethnicity ($F(4) = 10.5$, $p < .001$). When compared to New Zealand European, there was a mean difference of 13 years younger (95% C.I. 5.8, 20.1) for New Zealand Maori patients, 10 years younger (95% C.I. 3.1, 16.6) for Pacific Island patients and 10 years younger (95% C.I. 0.5, 19.8) for Asian patients.

Table 13.1 Comparison of baseline characteristics and outcomes across ethnicities

		NZE[13]	*NZM*[14]	*Pacific Island*	*Asian*	*Other*	*p value*
Hospital Site	*Hospital A*	67 (73%)	7 (8%)	10 (11%)	2 (2%)	6 (7%)	<.001
	Hospital B	56 (80%)	1 (1%)	0 (0%)	1 (1%)	12 (17%)	
	Hospital C	57 (50%)	14 (12%)	21 (18%)	10 (9%)	12 (11%)	
	Hospital D	25 (71%)	5 (14%)	0 (0%)	1 (3%)	4 (11%)	
Gender	*male*	114 (55%)	14 (52%)	17 (55%)	6 (43%)	14 (41%)	.542
	female	91(44%)	13(48%)	14(45%)	8 (57%)	20 (59%)	
Age mean (sd) (mean difference from NZE)		80 (11.7)	67 (13.6) (13yrs, p<.001)	70 (14.5) (10 yrs, p<.001)	70 (14.5) (10 yrs, p=.171)	79 (14.5) (0.8 yrs, p=.994)	< .001
Previous stroke		58 (28%)	9 (33%)	8 (26%)	3 (21%)	12 (35%)	.833
Cardiac Comorbidities		142 (69%)	23 (85%)	23 (74%)	8 (57%)	23 (68%)	.354
Diabetes		25 (12%)	7 (26%)	8 (26%)	1 (7%)	5 (15%)	.119
Respiratory comorbidities		22 (11%)	6 (22%)	7 (23%)	2 (14%)	4 (12%)	.242
Site of lesion	*cortical*	139 (68%)	21 (78%)	20 (65%)	12 (86%)	20 (59%)	.074
	subcortical	36 (18%)	1 (4%)	7 (23%)	1 (7%)	6 (18%)	
	other	19 (9%)	5 (19%)	3 (10%)	1 (7%)	2 (6%)	
	NAD	11 (5%)	0 (0%)	1 (3%)	0 (0%)	6 (18%)	
Domicile at 3 months	*public hospital*	9 (10%)	1 (6%)	1 (61%)	0 (0%)	1 (6%)	.524
	residential care facility	47 (50%)	4 (25%)	4 (31%)	3 (43%)	6 (35%)	

[13] New Zealand European

[14] New Zealand Maori

	home	39 (41%)	11 (69%)	8 (8%)	4 (57%)	10 (59%)	
CRT result	*strong*	60 (63%)	9 (56%)	8 (62%)	3 (42%)	11 (65%)	.753
	weak	21 (22%)	3 (19%)	2 (15%)	1 (14%)	4 (24%)	
	fail	14 (15%)	4 (25%)	3 (23%)	3 (43%)	2 (12%)	
Mortality		41 (20%)	3 (11%)	2 (7%)	0 (0%)	6 (18%)	.116
Confirmed pneumonia		28 (14%)	3 (11%)	3 (10%)	2 (14%)	3 (9%)	.911

13.3.3 Pneumonia.

The overall pneumonia rate was 27%. There was a higher risk of pneumonia with elder age, with each additional decade of life associated with 1.4 times higher risk in pneumonia (95% C.I. 1.1, 1.8, p = .011). Male patients were associated with 2 times higher risk in pneumonia (95% C.I. 1.0, 3.5, p = .043). Cardiac comorbidities were associated with 3.0 times higher risk of pneumonia (95% C.I. 1.4, 6.5, p = .005); while respiratory comorbidities were associated with 4.3 times higher risk of developing pneumonia (95% C.I. 2.0, 9.1, p < .001). There were differences between study sites, with a higher risk of pneumonia at Hospital C in comparison to both Hospital B and Hospital D [Hospital D vs. Hospital C, (odds ratio 0.3, 95% C.I. 0.09, 0.8), p = .021] and Hospital B vs. Hospital C 0.4 (95% C.I. 0.2, 0.9, p = .033).

Patients with confirmed pneumonia had higher mortality rates than patients without (35.6% vs. 10.9%, $X^2 = 24.46$, p < .001). Additionally, patients who developed pneumonia had significantly prolonged acute ward length of stays (median length of stay of 10 vs. 6 days, t = 3.91, p < .001). Of all patients who developed pneumonia (27%), the average number of days before commencing first course of antibiotics was 7.9 days after admission. Eleven percent of patients developed their first pneumonia once discharged and the average

number of days to development of pneumonia was 4 days if post-discharge pneumonia events were excluded. Thirty-five percent of patients experienced more than one pneumonia event of which 12% occurred in their initial inpatient admission and 23% occurred once discharged (with one patient experiencing further pneumonia events both in hospital and on discharge). Thirty seven percent of patients with pneumonia were nil by mouth and 63% patients were on oral diets. Six percent of the full cohort died from pneumonia (53% while in their initial inpatient admission, 47% following discharge).

13.3.4 Mortality.

Mortality rate was 16% with 44% of these deaths occurring during the hospital stay (90% acute ward, 10% rehabilitation ward). Forty two percent of patients died in a residential care facility, 7% at home and 7% following readmission to hospital. Reported causes of death were stroke 53%, pneumonia 27%, other 20%. Age was significantly associated with mortality ($X^2 = 9.92$, $p < .001$). Each additional decade of life was positively associated with 60% higher risk of mortality (95% C.I. 1.2, 2.3). ACE inhibitor use was significantly associated with mortality ($X^2 = 6.14$, $p = .011$); not taking ACE inhibitors was associated with 2.7 times higher risk of mortality (95% C.I. 1.2, 5.7). Cardiac comorbidity (previous cardiac surgery, idiopathic heart disease, atrial fibrillation or hypertension) was negatively associated with mortality with 2.0 times higher risk of mortality (95% C.I. 0.9, 4.3). Mortality rates did not differ significantly across sites (Hospital A 15%, Hospital B 17%, Hospital C 21%, Hospital D 6%).

13.3.5 Length of stay (LOS).

The median LOS (excluding those who died during admission) was 24 days with a median of six days on an acute ward, and a median of 31 days on a rehabilitation ward for

those who received rehabilitation. Fifty-seven percent of patients were accepted into an inpatient rehabilitation ward. Community-based rehabilitation was not documented and only 21% of patients returned home straight from an acute ward.

13.3.6 Domicile by 3 months.

By three months after their stroke, 45% of patients were living at home, 38% were in residential care, 16% were deceased and 1% was still in hospital. In this cohort, 19% of patients were readmitted within three months after their stroke. Causes of readmission were pneumonia 19%, stroke 15%, cardiac problems (e.g., chest pain, AF, CHF) 24%, orthopaedic 9%, other infection (e.g., UTI) 16% and other medical problems 17%.

13.3.7 Instrumental assessment use.

Referral rates for instrumental assessment (VFSS or FEES) were 13% (range 7%-18% across sites). Time to instrumental assessment was a mean of 6.5 days (range 1-30). Sixty seven percent of these patients received their instrumental assessment after developing pneumonia (Figure 13.1). There was a non-significant association between developing pneumonia and receiving an instrumental assessment (38% instrumental, 25% no instrumental, $X^2 = 2.44$, $p = .122$) with the odds of developing pneumonia 1.87 times higher if you had an instrumental assessment.

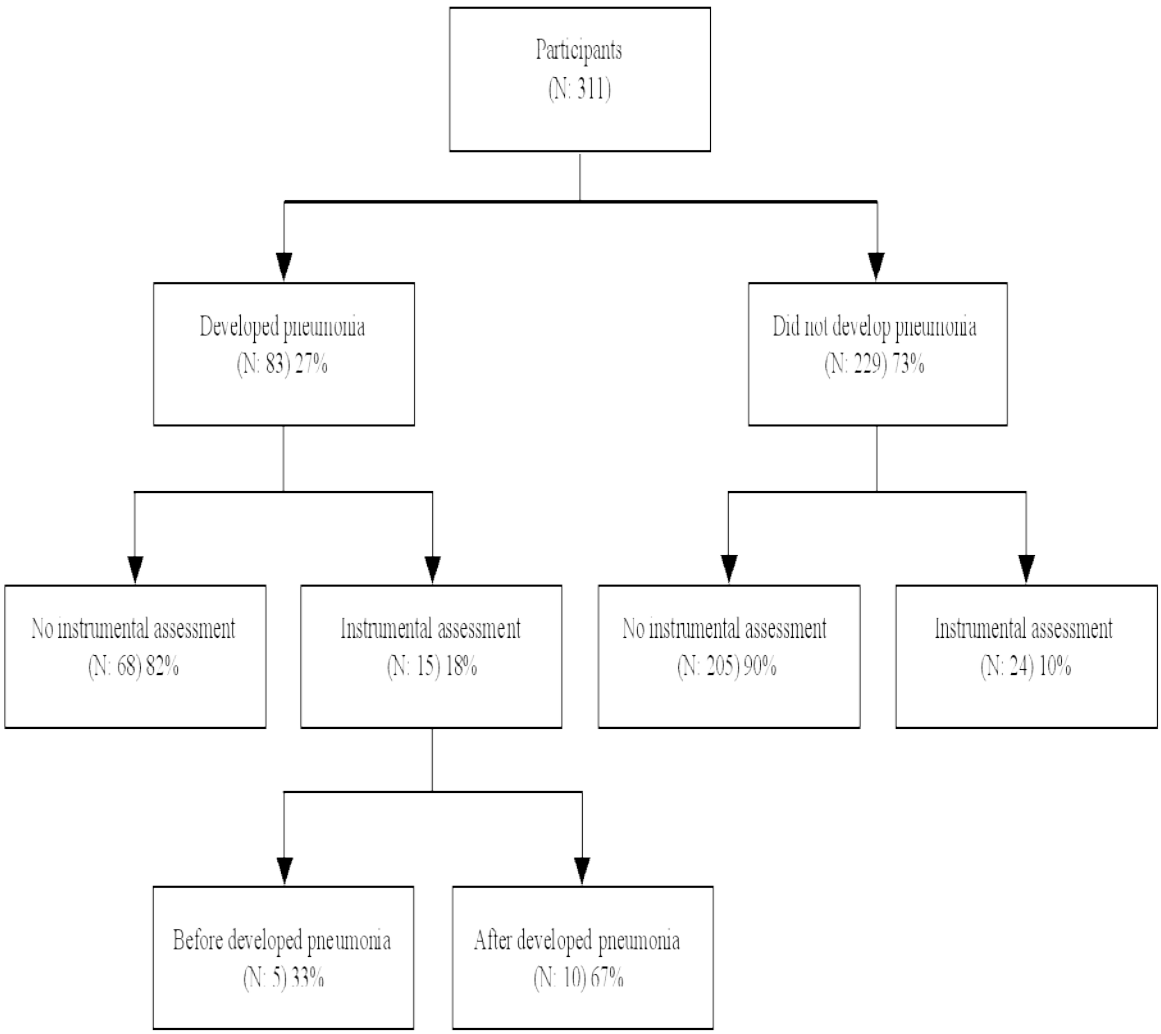


Figure 13.1 Instrumental assessment referrals and pneumonia

13.3.8 Cost implications (based on selected DHB data).

Three DHBs provided detailed information regarding costs of stroke admission and treatment of pneumonia. Although considerable differences were noted in costs between the three sites, the mean length of stay without pneumonia was 6 days (range 6.3-6.8). This rose to a mean of 10 days (range 10.0-10.1) if pneumonia was reported, with a 24-hour bed stay to the stroke unit costing on average $514.60 ($405.12-$589.43). The average overall cost

across sites for hospitalisation subsequent to stroke in 2011 was $9,946.41 (range $6,458-$13,066.87). This figure increased to an average of $13,800.46 (range $8,659-$22,319.84) when stroke was associated with pneumonia.

13.4 Comparative discussion

This prospective cohort study identified the characteristics and outcomes for patients with dysphagia after stroke in New Zealand with the purpose of comparing these data with a recent national stroke audit and benchmarking the outcomes for New Zealander's with dysphagia against published international data. The outcomes for New Zealand stroke patients with dysphagia were poor with a high risk of pneumonia and long hospital stays. Ethnicity was associated with younger age of stroke but no difference in functional outcome. Inversely, older age was associated with increased pneumonia and mortality. Pneumonia incurred significantly increased costs during hospitalisation. Caution must be taken when comparing one data set to another where different methodologies are used but careful comparisons are of interest as a means of benchmarking clinical services to international standards.

13.4.1 Comparison to national stroke data.

Patient characteristics between our dysphagic stroke group and The Stroke Foundation National Acute Stroke Audit 2009 (Stroke Foundation of New Zealand, 2010) appear similar (Table 13.2). The larger Pacific Island population in the dysphagia group (10% vs. 3%) perhaps reflects the impact of one of the hospital's population demographics (where 18% identified themselves as Pacific Islander). The dysphagic stroke group presented fewer comorbidities than the national data, perhaps reflecting the exclusion criteria of palliation.

Table 13.2 Comparison of baseline characteristics between the dysphagic stroke data and the national stroke data

	National Acute Stroke Audit Data 2009 (Stroke Foundation of New Zealand, 2010)	*Dysphagic Stroke data 2011*
Females	52%	53%
Mean Age	77	78
New Zealand European	-	66%
Maori	13%	9%
Pacific Island	3%	10%
Respiratory Comorbidities	-	13%
Diabetes	23%	15%
Previous Stroke	45%	29%
ACE inhibitor prescription	-	35%
Living a home	90%	86%

Inpatient rehabilitation provision was similar across New Zealand cohorts (dysphagic cohort 57%, National Acute Stroke Audit cohort 56%) but the proportion of patients who returned to their own home from acute hospital in the dysphagic group was less than the national data (dysphagic cohort 21%, National Acute Stroke Audit cohort 37%). The median LOS on acute wards is similar across cohorts (dysphagic cohort 6 days, National Acute Stroke Audit cohort 5 days) but duration of rehabilitation stay was not recorded in the national audit. The National Acute Stroke Services Audit 2009 found 14% of patients died during their acute hospital stay and of these 87% died within a week of admission. In our study, 16% died of whom only 44% of these were during their hospital stay and 56% were after discharge. Our acute ward mortality rate was only 7% with only 15% of these within a week of admission. These data are not surprising in view of the exclusion of palliative patients on admission and longer follow-up into the community in the current study. The high

incidence of death in residential care facilities (42% of all deaths) perhaps reflects the New Zealand trend for discharging palliative patients to residential care facilities rather than managing them in an acute hospital. Although palliation on admission was an exclusion criteria, many patients were deemed palliative after recruitment to the study.

13.4.2 Comparison to international data.

The association between dysphagia, aspiration pneumonia and mortality has attracted large-scale investigation and is well documented (Finlayson et al., 2011; Guyomard et al., 2009; Ingeman, Andersen, Hundborg, Svendsen, & Johnsen, 2011; Koennecke et al., 2011; WF Westendorp et al., 2011). International benchmarking is important for judging service delivery and there are studies that are comparable to the current data. The incidence of pneumonia in patients with dysphagia post-stroke can, however, be difficult to extrapolate from the literature for comparison with local data. Studies often use differing participant criteria for inclusion (acute vs. chronic, dysphagic vs. non-dysphagic) and differing criteria for diagnosis of pneumonia. Westerdorf and colleagues recently conducted a large systematic review and meta-analysis of literature (including 87 studies and 137817 patients) summarising post-stroke infection and found a 10% pneumonia rate in the general stroke population (WF Westendorp et al., 2011). This is comparable with the New Zealand general stroke data. A recent multi-centre retrospective cohort study of 8,251 stroke patients admitted to hospital in Canada found that 7% developed pneumonia (Finlayson et al., 2011). In this study, predictors for pneumonia included old age, male gender, stroke severity, dysphagia, respiratory comorbidities, cardiac comorbidities and previous level of independence (Finlayson et al., 2011). In a large, recent American study of 18,017 patients with stroke discharged from 222 hospitals, 4% of patients who were not screened for dysphagia developed pneumonia, 2% of patients who received and passed a dysphagia screen

developed pneumonia, and 7% of patients who failed a dysphagia screen developed pneumonia (Lakshminarayan et al., 2010). An unfortunate exclusion criteria for the study was patients who remained nil by mouth throughout their hospital stay perhaps excluding some of the most severe dysphagics and therefore those at higher risk of developing pneumonia. The pneumonia rates in this study are disproportionate low in comparison with those of Study VI, where all patients received a swallowing assessment and 26% developed pneumonia.

In comparison to these lower general stroke pneumonia rates, Martino and colleagues found seven studies that assessed incidence of pneumonia in stroke patients with dysphagia in their systematic literature review. In studies of acute patients, pneumonia rates ranged from 16% to 19% with the exception of one study with 33% (Martino et al., 2005). They hypothesise differences in patient acuity and definitions of pneumonia as the cause of the differences (Martino et al., 2005). The New Zealand general stroke pneumonia rates (New Zealand Acute Stroke Audit 10%) appear comparable to this international data (range 2-16%) (Finlayson et al., 2011; Martino et al., 2005; WF Westendorp et al., 2011), however pneumonia rates in our dysphagic cohort (27%) are at the high end of the range for patients with dysphagia after stroke (range 16-33%). Interestingly, Hilker and colleagues reported 44% of their stroke patients who were tube fed developed pneumonia (Hilker et al., 2003) and Langdon and colleagues found a 37% pneumonia rate in tube-fed stroke patients (Langdon et al., 2009). Tube feeding was not recorded in the current study, but a comparable 55% of patients placed NBM after swallowing assessment developed pneumonia but only 37% of patients who developed pneumonia were placed NBM after their swallowing assessment.

Koennecke and colleagues found mortality rates of 5.4% in their large cohort of 16,518 patients after stroke (Koennecke et al., 2011). In comparison, mortality rates were higher in our New Zealand studies (dysphagic cohort 16%, National Acute Stroke Services Audit cohort 14%). Without the exclusion of palliative patients, mortality in the dysphagia

cohort may in fact have been substantially higher. This would correspond more closely with international benchmarking where dysphagia and pneumonia lead to increased mortality rates. In a large community study (N=14,293), pneumonia resulted in a three-fold increased risk of 30-day death (Katzan et al., 2003).

Dysphagia has been associated with a 30% increase in LOS after ischemic stroke (Altman et al., 2010). A recent European study of 16,518 consecutive patients admitted with stroke found a median length of total hospital stay including rehabilitation of eight days (interquartile range 5-12 days) (Koennecke et al., 2011). Although differences in healthcare systems must be considered, this may suggest that our total LOS is high with a median of 24 days (interquartile range 9.5-42 days) if rehabilitation stay is included. The dysphagic cohort, who received inpatient rehabilitation, spent a long period of time (median of 31 days) in rehabilitation wards. In comparison, Altman and colleagues found a lower median LOS of 12.53 days for rehabilitation patients with dysphagia and a comparable 9.40 days for those without dysphagia (Altman et al., 2010). Unfortunately, they adjusted for age and sex but not stroke severity in their analysis making it difficult to conclude dysphagia as an independent factor. Overall stroke severity is a possible reason for this increased LOS associated with dysphagia. However, time taken treating secondary complications such as pneumonia leads to delays in transferring to rehabilitation and this must be considered. Increased LOS associated with medical complications and especially pneumonia is well documented (Ingeman et al., 2011). There was a significant association between pneumonia and increased acute ward LOS in our study.

13.4.3 Instrumental assessment.

Swallowing screening and bedside CSE underestimate aspiration and do not provide the diagnostic information required for informed dysphagia management decisions

(Smithard et al., 1998; Splaingard et al., 1988). Daniels and colleagues found 25% in their cohort of unselected acute stroke patients silently aspirated (Daniels et al., 1998). Instrumental assessment referral rates in this selected dysphagic cohort therefore appear extremely low (13%) suggesting that the majority of dysphagia management was occurring without accurate diagnostic information. Sixty percent of all instrumental assessments occurred after the development of pneumonia. This use of pneumonia as an indicator of dysphagia or aspiration and as a trigger for instrumental assessment referral suggests a 'wait and see' approach. With an increased risk of mortality and increased length of stay associated with the development of pneumonia after stroke (Altman et al., 2010; Schmidt et al., 1994), this clinical reasoning is unacceptable. Sixty-three percent of those who developed pneumonia were on oral diets perhaps indicating inappropriate dysphagia management. Interestingly, this may not be a local issue. In a recent UK survey of 68 SLTs across a mixture of adult settings, 69% had easy access to VFSS at work and 27% had easy access to VFSS at another local location yet only 49% of the SLTs reported using VFSS to make decisions about whether a patient should eat or drink (Cocks & Ferreira, 2013). When asked to rate factors that impacted decision-making about oral versus non-oral feeding, aspiration (amount, frequency and whether it was silent) was deemed important by only 86% of the SLTs. The introduction of strict clinical pathways that address the problems of identifying and monitoring silent aspiration and increased use of instrumental assessment may significant reduce the secondary complications for patients with dysphagia and the cost to the Health System.

13.4.4 Cost implications.

The financial implications of pneumonia have gained interest especially in the United States. In the 1990s Garon and colleagues, in a North American-based study, attempted to quantify the cost of pneumonia after stroke and found an additional burden of approximately

$10 000US per event and an average extended hospital LOS of seven days (Garon et al., 1996). In another large community study (N=14,293), pneumonia resulted in a three-fold increased risk of 30-day death and a calculated cost of stroke related pneumonia to the United States was approximately $459 million (Katzan et al., 2003). More recently, Wilson and Howe completed a large-scale review of nationwide medical records, again, in the United States (183,976 admissions). The hospital stay cost for a stroke patient who developed pneumonia was calculated at over $23,000US greater than that of a patient who did not develop pneumonia (Wilson & Howe, 2012). Overall the outcomes for dysphagic patients in this study were poor with high pneumonia rates, high mortality rates and lengthy rehabilitation ward stays. These data come with significant cost implications. Stroke admissions with a secondary complication of pneumonia led to an average increase in cost of 39% per patient across three DHBs in 2011. With an admission rate of 1310 patients referred for swallowing assessment in one of the research sites and a rate of pneumonia at 27%, the additional cost to this DHB alone was $1,363,177.40 in 2011.

Internationally, formal swallowing clinical pathways (Odderson et al., 1995) and swallowing screening (Hinchley et al., 2005) have been employed successfully to reduce pneumonia rates in patients after stroke. Preventative antibiotic prescription (WK Westendorp et al., 2012), ACE inhibitor use (Arai et al., 2005) and stringent oral cares (El-Solh, 2011; Langdon et al., 2009; Watando et al., 2004) also show promising results in pneumonia reduction. In light of the data presented in this study, New Zealand stroke services need to review current practice and focus on improving the prognosis for this vulnerable population group. In view of the health and cost implications, there needs to be a significant emphasis on the prevention of pneumonia rather than monitoring for it and treating it after it develops. Increased use of sensitive dysphagia assessment tools for the

identification of high-risk patients and increased attention to known predictors of pneumonia require priority attention.

13.4.5 Limitations.

It is well established that dysphagia is associated with poor functional outcomes and we would therefore expect dysphagic stroke outcome data to compare poorly with general stroke outcome data (Altman et al., 2010). The lack of a stroke severity measure in our study does, however, limit the interpretation of comparisons. It could be argued that patients with more severe strokes have dysphagia rather than dysphagia results to poorer outcomes. Clinically this distinction may be of little importance, as patients with dysphagia remain high-risk, incur high costs and require special attention.

There are some significant considerations in benchmarking against the data in this study. The current study excluded those provided with palliative care after admission to hospital. The concurrent experimental trial must be acknowledged as half of the cohort received the addition of CRT alongside standard care. Both of these factors could lead to skewed data in favour of improved outcomes in our dysphagic cohort. Our dysphagic patients were followed up for three months after stroke in comparison to the National Acute Stroke Audit 2009 where patients were only reviewed until discharge from acute hospital. This may lead to increased reporting of secondary complications over time in our cohort.

13.4.5 Summary.

The outcomes for stroke patients with dysphagia in New Zealand are poor with high pneumonia rates and long hospital stays. The outcomes for stroke patients with dysphagia in New Zealand compare poorly to international data with an unacceptable rate of pneumonia of 27%.

PART G: FUTURE RESEARCH AND CONCLUDING REMARKS

CHAPTER FOURTEEN

FUTURE RESEARCH AND FINAL REMARKS

14.1 Future Research

There is a strong relationship between disordered swallowing and impaired cough in patients with neurological disease (Bolser, 2010). Cough testing holds great promise in the endeavor to advance dysphagia assessment. Moreover, in view of the differing neurophysiological pathways and autonomous impairment in disease, assessment of cough reflex sensitivity, reflexive cough strength, voluntary cough and voluntary cough strength may provide different information and have independent value. Building interest in urge-to-cough ratings holds promise in assessing the integrity of cortical components of cough after a neurological event. The development, validation and clinical utility of a combined cough test protocol would be clinically valuable. This may allow the clinician to understand a patient's reflexive cough sensitivity and strength as well as their cortical control of cough in order to make informed management decisions.

Objective assessments of laryngeal sensitivity (e.g., FEESST) and voluntary cough strength (e.g., airflow measures) have merit but require expertise and specialist equipment (Aviv et al., 1998; Smith-Hammond et al., 2009). Further research into the validation of subjective assessments of cough (CRT and subjective cough strength judgements) against these objective measures would add value to the clinical field. Validation of CRT against FEESST would allow CRT to be compared to laryngeal sensitivity. CRT presumably reaches both the upper and lower airways and this comparison will add to the developing understanding of the effects of citric acid inhalation on the airway. The difference between sensitivity of the SLN-innervated vocal cords and the RLN-innervated sub-glottis impacts on timeliness, and therefore efficiency, of airway protection. It is beneficial to understand whether CRT stimulates supra-glottically or both supra- and sub-glottically and whether

time before first cough is indicative of level of airway stimulated or purely overall speed and efficiency of the sensory pathway. Subjective latency and strength of cough response to aspiration was recorded in Study II. Speed of initiation of cough in response to CRT was not recorded and may have added interest. It is possible that those patients who do not cough until later in the 15-second period have subtle sensory impairments. Visual observation of cough during CRT under endoscopic view may also allow further understanding of the presence or absence of an expiratory reflex prior to the series of coughs during CRT. If certain thresholds of citric acid trigger expiratory reflex prior to a cough reflex then the initial reflexes most certainly occur prior to cortical involvement and represent a purely brainstem response as the Addington group claim of their methods (W. Addington, Stephens, & Gilliland, 1999).

Type of cough triggered during an aspiration event and with different methods of CRT deserves further study. As discussed previously, many types of cough are impaired after neurological disease. The type of cough triggered by an aspiration event has not been confirmed. Large amounts of aspiration or aspiration of highly toxic substances (e.g., spice, alcohol, citric) may trigger a strong, brisk brainstem controlled reflexive response e.g., an expiratory reflex followed by a laryngeal cough reflex. However, small amounts of aspiration or the accumulation of saliva may gradually trigger an urge-to-cough and a cortically modulated evoked cough response. In view of the high proportion of cortical strokes, it could be argued that cortically modulated cough is most commonly impaired and more relevant that a pure brainstem reflex. Urge-to-cough is reduced with old age and aspiration pneumonia suggesting a supramedullary dysfunction breaking down the desire to cough and motivation to cough sufficiently to compromise optimal health (Davenport, 2008; S. Ebihara et al., 2011; Yamanda et al., 2008). If patients with cortical stroke suffer from this impairment, they may be at risk of both silent aspiration and aspiration pneumonia yet

still cough if the stimuli is strong enough to trigger a brainstem reflex. In fact, Hegland and colleagues concluded that reflex cough in the conscious person can always involve supramedullary activation even at high concentration levels (Hegland et al., 2012).

This thesis has uncovered further questions regarding the reliability and validity of subjective cough judgement; an area relatively untouched in dysphagia assessment. We did not address validity of subjective cough judgement in this thesis and future studies where participants are rating coughs of a known strength would be valuable. Study III and IV revealed cues used by clinicians such as general health status and a bias towards visual cues. Future investigation may reveal which of these cues proves the most clinically useful and therefore guide future undergraduate and in-house training.

Further work is justified in refining the CRT methodology and protocol. The advantage of CRT is that it can be standardised and therefore with careful protocol can avoid the interpretative variance of many subjective components of bedside clinical swallowing evaluation. Citric acid concentrations used in this study provide a useful working range but further testing of other concentrations may improve detection of subtle sensory deficits. Normative data has proven difficult secondary to the variance of cough response in the healthy population and a threshold at which you are at risk of silent aspiration appears more useful (Monroe et al., 2010). However, there will continue to be a group of people who do not cough on CRT who, perhaps unless also severely dysphagic, may not need further management. The effect of gender on cough threshold is well established and this may need to be accounted for in CRT protocols. The impact of medications on cough thresholds is also well documented but it is uncertain how this impacts positively or negatively on the silent aspiration risk of a patient with dysphagia. Further research is needed to provide clarity on both the impact of medication on silent aspiration and on the clinical interpretation of cough threshold results in these people.

It could be argued that methodology that focuses on the dispersion of irritant to the larynx rather than the lower airways may be appropriate in the detection of silent aspiration. While citric acid and capsaicin continue to produce coughs during bilateral anesthesia of iSLN, tartaric acid cough is abolished (W. Addington, Stephens, & Goulding, 1999; Stockwell et al., 1993). Different agents therefore perhaps have different merits depending on whether the tester wants to know specifically about laryngeal sensitivity versus overall airway responsiveness. Nebuliser choice is clearly important for standardisation and thresholds will change if equipment changes. This is not ideal in a constantly changing healthcare system where resources are sparse and providers change regularly. Research into the impact of nebuliser, flow rate and particle size on thresholds in dysphagic patients would aid our understanding of the true impact in this specific use of CRT. Should the passive respiration approach continue to be used in CRT in the dysphagic population, further investigation on the effect on individual's respiration rate, sitting position and time of day should also be considered on both CRT threshold and cough strength judgement. Studies on the repeatability of CRT in patients with dysphagia are needed. In healthy participants, repeatability has been proven and varies only by one threshold across time but it is unknown what threshold change indicates a clinically relevant change in function (Bickerman et al., 1957). The study of intra-subject variation in a dysphagic population is required.

Given the positive validation data presented in this thesis, further investigation of the clinical use of CRT is warranted. Integration of CRT results into multidisciplinary clinical decision-making and clinical pathways is a worthy research avenue in order to further explore the potential of CRT for influencing clinical outcomes. Exploring the use of CRT in different dysphagic populations would also be of value. This thesis focused primarily on acute stroke but cough sensitivity may differ across dysphagic populations and CRT may prove more valuable in some conditions compared with others. If some dysphagic population groups

such as patients with COPD have heightened cough sensitivity, what threshold of citric acid indicates deterioration in swallowing safety? Does a different level of citric acid indicate silent aspiration risk in these populations? Hammer and Barlow found diminishing laryngeal sensitivity in patients with Parkinson's disease in line with disease progression (Hammer et al., 2010). CRT may have potential as a monitoring technique in community settings to assess deterioration of function, or in the case of acute neurological disease, to monitor recovery.

14.2 Final Remarks

A valid, reliable bedside test for 'silent aspiration' holds great value for acute dysphagia management. This research programme has contributed to our understanding of the use of CRT in the identification of silent aspiration. Cough reflex testing with cough strength judgement is a valid and reliable tool for identifying silent aspiration in patients with dysphagia. CRT results are significantly associated with aspiration response on instrumental assessment and lower concentrations of citric acid provide a better predictive measure of silent aspiration. CRT methodology described in this thesis is appropriate for the neurological patient and sensitivity and specificity values of CRT for identifying silent aspiration are sufficient to endorse incorporation into clinical protocols. The addition of a measure of reflexive cough strength may add to clinical assessment but specific training is required to reach adequate reliability. Inclusion of CRT alone was not shown sufficient to change clinical outcomes and integration of CRT into clinical pathways may prove more successful. Further research evaluating the addition of CRT to a comprehensive CSE test battery would add greatly to the field of dysphagia assesssment.

Adequate swallowing assessment remains a problem in dysphagia management with sub-optimal identification of silent aspiration by CSE, low instrumental assessment rates,

and at a national level, high pneumonia rates when compared with published international data. Further work is required to ensure improved assessment practices such as CRT lead to changes in management practices that are sufficient to reduce the secondary complications of dysphagia.

APPENDICES: INFORMATION SHEETS AND CONSENT FORMS

INFORMATION SHEET

Research Title:

Cough reflex testing in swallowing assessment.

Primary / Principal Researcher:

Anna Miles

PhD Student, University of Canterbury

Co-Investigators:

Mary McFarlane

MSc Student, University of Canterbury

Speech and Language Therapy

North Shore Hospital, Waitemata District Health Board

Maggie-Lee Huckabee PhD

Senior Lecturer, Department of Communication Disorders, University of Canterbury

Senior Researcher, Van der Veer Institute for Parkinson's and Brain Research

Jacqueline Allen MBChB, FRACS

Dept of Otolaryngology, North Shore Hospital,

Shakespeare Rd, Takapuna, Auckland, 0740 New Zealand

Introduction and aims of the project:

You/ your whanau member/ friend has been asked to participate in a research project that will evaluate the use of a cough test as part of a swallowing assessment. You have the right not to participate in the study, or subsequently withdraw from this study at any time. Any decision not to participate will not affect current, continuing or future health care at this or any other health care facility.

In many patients with swallowing problems the ability to cough when food enters the lungs will be impaired. Currently there is no way to reliably identify patients who have no cough and therefore no way of protecting their airway if food/drink slips down the wrong way (aspiration). The data from this study will be used to develop a method of identifying these 'at risk' patients, and hence improving their management.

The aim of this project is to validate a cough test against accepted measures of swallowing and sensation in the throat. The cough test involves placing a facemask over the nose and mouth, and then quietly breathing in a mist that contains a substance called citric acid. This substance may make you cough. Citric acid has been used for the purpose of eliciting cough since the 1950s, with no adverse effects. The assessment of aspiration and sensation in the throat will involve the use of the well-established test called 'flexible endoscopy'. This involves looking at your throat with a camera through a small tube placed in your nose. This assessment is part of routine clinical care for many patients and may be recommended if you participate in the study or not. If your swallowing or cough reflex is identified as being impaired as a result of a new stroke you will be reassessed using the cough test and flexible endoscopy. Reassessment will take place every four days for up to 3 weeks from your first assessment. Further reassessment will be discontinued before 3 weeks if safe swallowing and a normal cough reflex is identified on re-assessment during this period. Your ward speech language therapist will be provided with the results of all your assessments and will then use this information to plan your treatment.

Participant selection:

You/ your Whanau member/ friend has been identified as a potential participant for this study since being referred to a speech-language therapist with suspected or confirmed

swallowing difficulties. Upon your consent, you will be selected for this study. The study will include a total of 100 participants. We acknowledge that you may wish to discuss this project with your Whanau before consenting.

The research procedure:

If you agree to participate in the study, the following will occur:

1. Once you/ your Whanau member/ friend has signed the consent form to participate in the study, you will be seen by the researchers for a number of assessments.
2. **Cough Reflex Testing-**
   i) This test takes a maximum of 10 minutes to complete.
   ii) You will be given a facemask, which is attached to a device that turns water into a mist, called a nebuliser.
   iii) A small quantity of citric acid (of various doses) will be mixed into water. You will be asked to quietly breathe in through the mask for a period of 15 seconds
   iv) The mist you inhale may make you feel like coughing. You will be asked to cough if you feel the need to cough, but not to if you don't.
   v) At each dose, the test will be repeated two more times to evaluate how consistently you cough when you breathe in the mist.

   iv) This will be repeated for 3 different doses of citric acid (0.8M, 0.6M, 0.4M) to determine what concentration of citric acid makes you cough.
3. **Flexible Endoscopic Study of Swallowing-**

   This test takes a maximum of 20 minutes to complete.
   a. One of the researchers, trained in this procedure, will place a flexible endoscope through your nose. This allows the clinicians to view the inside of your throat and voice box. The scope sits above the voice box during the test.
   b. You will be asked to drink and eat small quantities of food and liquid. Your researcher will support you through the assessments in accordance with the hospital's Tikanga Best Practice Policy and the option of a Karakia prior to assessment will be offered

4. If you have had a stroke and food/ fluid goes into your airway or your cough reflex is weak on your first assessment, you will be asked to repeat the assessments every 4 days to watch for improvement. This will continue for 3 weeks or until your swallow and cough have improved.

5. If you consent to the study, your ward speech-language therapist will be provided with the results of the assessments to help in the management of your swallowing difficulties.

Risks and Benefits:

It is possible that your overall outcomes may be improved because your ward therapist will be provided with more information about your cough, swallowing and sensation in your throat. There are no documented adverse side effects of the cough test. Nevertheless, it will be performed by trained research clinicians who will monitor you for any difficulty during the test. The other test, (Flexible Endoscopic Study of Swallowing) is considered a safe, well-recognised assessment tool. When carried out by experienced clinicians side effects are rare but may include nosebleed, and fainting. Some patients experience discomfort as the scope is inserted.

Participation:

If you do agree to take part in this study, you are free to withdraw at any time, without having to give a reason. This will in no way affect any future care or treatment.

Your participation in the study will be stopped should any harmful effects appear or if you feel it is not in your best interest to continue.

Confidentiality:

Research findings will be presented at international research meetings and submitted for publication in peer-reviewed journals. Additionally, research findings will be made available to the local medical community through research presentations and regional forums. However, no material that could personally identify you will be used in any reports on this study. Consent forms will be kept in a locked filing cabinet in the speech and language therapy departments at the hospital or will be stored on password-protected computers. Research data will be stored for a period of ten years after data collection is complete, at which time they will be destroyed. With your permission, data from this study may be used in future related studies, which have been given ethical approval from the Northern Y Ethic Committee.

Results:

If requested, you will be offered copies of the publications that arise from this research. However, you should be aware that a significant delay may occur between completion of data collection and completion of the final report. Alternatively, or in addition, you can choose to have the results of the study discussed with you personally by the lead investigator.

Questions:

You may have a friend or whanau support to help you understand the risks and/or benefits of this study and any other explanation you may require.

Please contact your speech and language therapist if you require any further information about the study. Alternately, the primary researchers listed on the front page of this information sheet can be contacted during work hours at the numbers provided.

If you need an interpreter, this can be provided.

To ensure ongoing cultural safety Nga Kai Tataki - Maori Research Review Committee Waitemata DHB encourage those who identify themselves as Maori and who are participating in health research or clinical trials to seek cultural support and advice from either Mo Wai Te Ora – Maori Health Services or their own Kaumatua or Whaea. For assistance please contact the Services Clinical Leader for Mo Wai Te Ora – Maori Health on 09 486 1491 ext: 2324 or the Maori Research Advisor on 09 486 1491 ext: 2553

If you have any queries or concerns about your rights as a participant in this study, you may wish to contact a Health and Disability Advocate, telephone: Auckland Central: 09 525 2700 or 0800 555 050. Free Fax (NZ wide): 0800 2787 7678 (08002SUPPORT). Email (NZ wide): advocacy@hdc.org.nz.

UC UNIVERSITY OF CANTERBURY
Te Whare Wānanga o Waitaha
CHRISTCHURCH NEW ZEALAND

Waitemata District Health Board
Te Wai Awhina

Cough Reflex Testing in Swallowing Assessment

English	I wish to have an interpreter.	Yes	No
Maori	E hiahia ana ahau ki tetahi kaiwhakamaori/kaiwhaka pakeha korero.	Ae	Kao
Samoan	Oute mana'o ia iai se fa'amatala upu.	Ioe	Leai
Tongan	Oku ou fiema'u ha fakatonulea.	Io	Ikai
Cook Island	Ka inangaro au i tetai tangata uri reo.	Ae	Kare
Niuean	Fia manako au ke fakaaoga e taha tagata fakahokohoko kupu.	E	Nakai

I, _____, have read and I understand the Information Sheet about taking part in this study designed to collect information about the usefulness of cough reflex testing. I have had the opportunity to discuss this study. I am satisfied with the answers I have been given.

I have had this project explained to me by _____.

- I understand that taking part in this study is voluntary (my choice) and that should I withdraw from the study, this will in no way affect my current, continuing or future health care. I understand that I can withdraw from the study at anytime during the assessment phase. Once my assessments are completed, my details will be anonymously collated and will no longer be able to be identified or withdrawn.

Cough Reflex Testing in Swallowing Assessment

- I understand my assessments will be recorded for the purpose of analysis only. Recorded material will be stored in a locked office and on a password-accessed computer.
- I understand that the information obtained from this research may be published. However, I understand that my participation in this study is confidential and that no material that could identify me will be used in any reports on this study.
- I understand that the investigation will be stopped if it should appear harmful to me and I know who to contact if I have any side effects to the study or have any questions about the study.
- I understand the potential risks of participation in the study as explained to me by the researcher.
- I have had time to consider whether to take part.

I wish to receive a copy of the results. YES / NO

Address to send results:_____

I, _____ hereby consent to take part in this study.

Date_____

Signature _____

Signature of researcher_____

Name of researcher_____

Name of primary researchers and contact phone numbers:

Name: Anna Miles, Mary McFarlane, Dr. Jacqui Allen, Dr. Maggie-Lee Huckabee

Appendix 1 Information Sheet/ Score Sheet

Inter-rater reliability of subjective judgment of cough strength during a cough reflex test

Please read the following before completing the questionnaire.

You are invited to participate in the above research project by completing the following questionnaire. The aim of the project is to investigate the agreement between speech-language therapists in subjectively judging the strength of a patient's cough. We are currently completing a research project which evaluates the usefulness of cough reflex testing for reducing chest infections in patients with stroke. Participants in this study receive concentrations of citric acid in a mist through a face mask to assess cough response. The participating therapists are asked to rate the participants' cough response as a strong, weak or no cough. In order for this test to be useful clinically, it is important to ascertain the reliabilty of therapist's judgements of a weak versus a strong cough.

This reliability study is being carried out by Anna Miles under the supervision of Dr Maggie-Lee Huckabee, who can be contacted at XXX. They will be pleased to discuss any concerns you may have about participation in the project. This project has been reviewed and approved by the Department of Communication Disorders and the UC HEC Low Risk Approval process.

The questionnaire is anonymous, and you will not be identified as a participant. You may

withdraw your participation, including withdrawal of any information you have provided, until your questionnaire has been added to the others collected. Because it is anonymous, it cannot be retrieved after that.

By completing the questionnaire it will be understood that you have consented to participate in the project, and that you consent to publication of the results of the project with the understanding that anonymity will be preserved

Inter-rater reliability of subjective judgment of cough strength during a cough reflex test

You will be shown a series of 10 video clips of patients completing a cough reflex test. Please rate the cough response as a strong, weak or no cough by circling your chosen rating. After a break, you will be shown the same 10 video clips in a different order and will be asked to rate the cough responses again.

Key
strong cough = ***2 or more strong coughs***
weak cough = ***2 or more weak coughs***
no cough = ***less than 2 coughs produced.***

Note: a throat clear is not classified as a cough.

1st Viewing

Example	strong	weak	no cough
video clip 1	strong	weak	no cough
video clip 2	strong	weak	no cough
video clip 3	strong	weak	no cough
video clip 4	strong	weak	no cough
video clip 5	strong	weak	no cough
video clip 6	strong	weak	no cough
video clip 7	strong	weak	no cough
video clip 8	strong	weak	no cough
video clip 9	strong	weak	no cough
video clip 10	strong	weak	no cough

2nd Viewing

Example	strong	weak	no cough
video clip 1	strong	weak	no cough
video clip 2	strong	weak	no cough
video clip 3	strong	weak	no cough
video clip 4	strong	weak	no cough
video clip 5	strong	weak	no cough
video clip 6	strong	weak	no cough
video clip 7	strong	weak	no cough
video clip 8	strong	weak	no cough
video clip 9	strong	weak	no cough
video clip 10	strong	weak	no cough

Thank you for your participation.

Appendix 1 Information Sheet/ Score Sheet

Inter-rater reliability of subjective judgment of cough strength during a cough reflex test

Please read the following before completing the questionnaire.

You are invited to participate in the above research project by completing the following questionnaire. The aim of the project is to investigate the agreement between speech-language therapists' subjective judgment of the strength of a patient's cough. We are currently completing an HRC funded research project which evaluates the usefulness of cough reflex testing for reducing chest infections in patients with stroke- 'Identifying Silent Aspiration after Stroke using Cough Test Testing' Ethics Approval Number NTY/09/11/113). This research project forms part of my PhD at University of Canterbury under the supervision of Dr Maggie-Lee Huckabee. Research investigators include myself, Dr. Maggie-Lee Huckabee, Helen McLauchlan (Professional Leader- Counties Manukau DHB), Dr Alan Barber (Consultant Neurologist- Auckland City Hospital) and Dr Edward Wong (Consultant Neurologist- Middlemore Hospital). All inpatients referred to stroke services at Middlemore Hospital, Auckland City Hospital, North Shore Hospital and Christchurch Public Hospital and referred for swallowing evaluation in a 12 month period are being approached for participation in the study. Those participants who agree to participate are randomly assigned to either a 1) standard evaluation group or 2) standard evaluation with inclusion of cough testing. For those in the experimental group, citric acid

in a mist will be inhaled through a face mask to assess cough response. Clinicians are encouraged to use these results to contribute to clinical decision making. Outcomes for both groups are being measured by chest infection rates at 3 months and other clinical indicators of swallowing impairment. If successful in reducing complications associated with stroke, this test can be easily implemented without significant cost or resources and consequently reduce the impact of stroke on health status and quality of life. The participating therapists are specifically asked to rate the participants' cough response as a pass, weak or fail. In order for this test to be useful clinically, it is important to ascertain the reliabilty of therapist's judgements of a weak versus a strong cough.

By completing the questionnaire it will be understood that you have consented to participate in the project, and that you consent to publication of the results of the project with the understanding that anonymity will be preserved. Participation in the study requires that you view 10 video clips of patients undergoing cough reflex testing (approx 10 sec in duration each) and provide a subjective judgment on the 'strength' of the cough response observed. The total time for completion of the study should not exceed 20 minutes.

The questionnaire is anonymous, and you will not be identified as a participant. You may withdraw your participation, including withdrawal of any information you have provided, until your questionnaire has been added to the others collected. Because it is anonymous, it cannot be retrieved after that. The data will be available only to the listed researchers below and will be stored in a locked filing system for 10 years before being destroyed by Dr. Huckabee.

This reliability study is being carried out by Anna Miles, who can be contacted a.miles@auckland.ac.nz under the supervision of Dr Maggie-Lee Huckabee maggie-lee.huckabee@canterbury.ac.nz).

They will be pleased to discuss any concerns you may have about participation in the project. This project has been reviewed and approved by the Department of Communication Disorders and the UC HEC Low Risk Approval process.

Inter-rater reliability of subjective judgment of cough strength during a cough reflex test

General Questions:

1) How many years of clinical experience do you have?
_____

2) How many years of dysphagia experience do you have (if different)_____

3) What is your primary caseload type:
☐ Adult
☐ Paediatric
☐ Neurology
☐ ENT/ ORL

Other:
_____

4) Have you had any previous training on cough physiology/ judgement (describe):

_____
__

5) Do you use a cough reflex test clinically?
_____

6) Are you aware of having a hearing or visual impairment that may hinder your ability to hear the video clips? _____

Qualitative Data Collection:

Do you have any qualitative comments about your experience in interpreting the videos?

Please rate the cough response as present or absent and then strong or weak.

strong cough = *2 or more strong coughs*
no cough = *less than 2 coughs produced.*

weak cough = *2 or more weak coughs*
Note: a throat clear is not a cough.

	1st Score		2nd Score	
	Present	or Absent	Strong	or Weak
example	present	absent	strong	weak
video clip 1	present	absent	strong	weak
video clip 2	present	absent	strong	weak
video clip 3	present	absent	strong	weak
video clip 4	present	absent	strong	weak
video clip 5	present	absent	strong	weak
video clip 6	present	absent	strong	weak
video clip 7	present	absent	strong	weak
video clip 8	present	absent	strong	weak
video clip 9	present	absent	strong	weak
video clip 10	present	absent	strong	weak

Thank you for your participation.

INFORMATION SHEET

Research Title:

Cough Testing after Stroke

Primary / Principal Researcher:

Helen McLauchlan
Professional Leader Speech and Language Therapy
Middlemore Hospital, Counties Manukau District Health Board

Co-Investigators:

Anna Miles
Department of Speech and Language Therapy
Auckland Hospital, Auckland District Health Board

Maggie-Lee Huckabee PhD
Senior Lecturer, Department of Communication Disorders, University of Canterbury
Senior Researcher, Van der Veer Institute for Parkinson's and Brain Research

Edward Wong MD
Department of Medicine
Middlemore Hospital, Counties Manukau District Health Board

Alan Barber MD
Department of Medicine
Auckland Hospital, Auckland District Health Board

Introduction and aims of the project:

You are invited to participate in a research project that will evaluate the use of a cough reflex test for decreasing your risk of chest infection. You have the right not to participate in the study, or subsequently withdraw from this study at any time. Any decision not to participate will not affect your current, continuing or future health care at this or any other health care facility.

In many patients with neurological problems (e.g., stroke) the ability to cough when food enters the lungs will be affected. Currently there is no way to reliably identify patients who have no cough and hence no way to protect the airway if food/drink slips down the wrong way. The data from this study will be used to develop a method of identifying these 'at risk' patient groups, and hence improving their management.

The aim of this project is to evaluate health outcomes in two groups of patients. One group will receive routine assessment of swallowing. One group will receive the same assessment but with the inclusion of a simple cough reflex test. This cough test involves placing a facemask over your nose and mouth, and then passively breathing in a mist that contains a substance called citric acid that may make you cough. Citric acid has been used for the purpose of eliciting cough since the 1950s, with no adverse effects. The speech language therapist that is evaluating your swallowing will then use this information to plan your treatment.

Participant selection:

You have been identified as a potential participant for this study since you have been admitted to hospital because of a suspected or confirmed stroke and have been referred to a speech and language therapist for swallowing evaluation. Upon your consent, you will be selected for this study if you are able to breath for yourself (ie…are not on a breathing machine). The study will include a total of 300 participants who have been

admitted with stroke. Half of these participants will be randomly assigned to receive the cough test; the other half will receive a standard clinical assessment as is currently completed. We acknowledge that you may wish to discuss this project with your Whanau before consenting.

The research procedure:

If you agree to participate in the study, the following will occur:

1. Once you have signed the consent form to participate in the study, you will be assigned a research participant number and an experimental group (cough or no cough group).

2. Regardless of which group you are assigned to, your speech and language therapist will evaluate your ability to swallow as she would normally do in accordance with the hospital's Tikanga Best Practice Policy. She may ask you to move the muscles of your face, mouth and throat; and then may ask you to eat and drink some carefully selected foods and liquids. This evaluation will be completed as part of standard hospital care after stroke and is not influenced by your participation in this study. As with all swallow assessments, the option of a Karakia prior to assessment will be offered.

3. If you are assigned to the group that does not receive cough testing, you do not need to do anything else for this study.

4. If you are assigned to the group that receives the cough testing, this assessment will then follow the routine examination. You will be given a facemask, which is attached to a device that turns water into a mist, called a nebuliser. A small quantity of citric acid, or saline will be mixed into the water. You will be asked to quietly breathe in through the mask for a period of 15 seconds.

5. The mist you inhale may make you feel like coughing. You will be asked to cough if you feel the need to cough, but not to if you don't.

6. If you cough, the facemask will be taken off to allow you to relax. The test will be repeated two more times to evaluate how consistently you cough when you breathe in the mist.

7. If you *do not* cough on 2 of 3 presentations of the mist, the test will be finished.

8. If you *do* cough on 2 of 3 trials, the test will continue with new instructions. You will be asked to try to suppress or stifle the cough as much as possible.

9. This will also be repeated two more times.

10. Your speech and language therapist will use this information to plan your treatment. You will not need to do anything else.

Outcome Measurements:

Three months time after your evaluation, a researcher will review your medical record to evaluate if you had any complications related to your swallowing during your hospital stay and in the time after your discharge. This researcher will look specifically at any formal tests you have had of your swallowing (x-rays), what foods and liquids you were recommended, if you have had any antibiotics for chest infections, or if you were re-admitted to hospital after your discharge.

Risks and Benefits:

There will be no proven benefit to you from participation in this study. For those who do not receive the cough testing, your evaluation and management will proceed as if you were not involved in the study. For those who receive the cough testing, it is possible that your overall outcomes may be improved because the therapist who evaluated you has more information about your cough. There are no documented adverse side effects of cough challenge. Nevertheless, the cough challenge will be performed by trained research clinicians who will monitor you for adverse signs during the test.

Participation:

If you do agree to take part in this study, you are free to withdraw at any time, without having to give a reason. This will in no way affect any future care or treatment. Your participation in the study will be stopped should any harmful effects appear or if you feel it is not in your best interest to continue.

Confidentiality:

Research findings will be presented at international research meetings and submitted for publication in peer-reviewed journals. Additionally, research findings will be made available to the local medical community through research presentations and regional forums. However, no material that could personally identify you will be used in any reports on this study. Consent forms will be kept in a locked filing cabinet in the speech and language therapy departments at the hospital or will be stored on password-protected computers. Research data will be stored for a period of ten years after data collection is complete, at which time they will be destroyed. With your permission, data from this study may be used in future related studies, which have been given ethical approval from the Northern Y Ethic Committee.

Results:

If requested, you will be offered copies of the publications that arise from this research. However, you should be aware that a significant delay may occur between completion of data collection and completion of the final report. Alternatively, or in addition, you can choose to have the results of the study discussed with you personally by the lead investigator.

Questions:

You may have a friend or whanau support to help you understand the risks and/or benefits of this study and any other explanation you may require. Please contact your speech and language therapist if you require any further information about the study. Alternately, the primary researchers listed on the front page of this information sheet can be contacted during work hours at the numbers provided.

If you need an interpreter, this can be provided.

If you would like ADHB Maori Support please contact- Mata Forbes, Maori Health Service, Admin Suite, Auckland City Hospital on (09) 307 4949 ext. 23939 or mobile 021 348 432. For CMDHB Maori Support please contact- Devi-Ann Hall. For WDHB Maori Support please contact Mo Wai Te Ora, Maori Health Services, North Shore Hospital, Te Raki Pai Whenua, (09) 486 8324 ext. 2324. For CDHB Maori Support please contact Samantha McFedries.

If you have any queries or concerns about your rights as a participant in this study, you may wish to contact a Health and Disability Advocate, telephone:

Auckland Central 09 525 2700 or 0800 555 050.

Free Fax (NZ wide): 0800 2787 7678 (08002SUPPORT)

Email (NZ wide): advocacy@hdc.org.nz

Cough Testing after Stroke

English	I wish to have an interpreter.	Yes	No
Maori	E hiahia ana ahau ki tetahi kaiwhakamaori/kaiwhaka pakeha korero.	Ae	Kao
Samoan	Oute mana'o ia iai se fa'amatala upu.	Ioe	Leai
Tongan	Oku ou fiema'u ha fakatonulea.	Io	Ikai
Cook Island	Ka inangaro au i tetai tangata uri reo.	Ae	Kare
Niuean	Fia manako au ke fakaaoga e taha tagata fakahokohoko kupu.	E	Nakai

I, _____, have read and I understand the Information Sheet dated _____ for volunteers taking part in the study designed to collect information about the usefulness of cough reflex testing. I have had the opportunity to discuss this study. I am satisfied with the answers I have been given.

I have had this project explained to me by _____.

I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time and this will in no way affect my current, continuing or future

health care or my academic progress if I am a university student. I understand that if I choose to withdraw from the study, I may also withdraw all information that I have provided.

Cough Reflex Testing

I understand that the information obtained from this research may be published. However, I understand that my participation in this study is confidential and that no material that could identify me will be used in any reports on this study.

I understand that the investigation will be stopped if it should appear harmful to me and I know who to contact if I have any side effects to the study or have any questions about the study.

I understand the potential risks of participation in the study as explained to me by the researcher.

I understand the compensation provisions for this study.

I have had time to consider whether to take part.

I wish to receive a copy of the results.
YES / NO

I, _____ hereby consent to take part in this study.

Date_____
Signature _____
Signature of researcher_____
Name of researcher_____
Name of primary researcher and contact phone numbers:
Name: Helen McLauchlan at Middlemore Hospital Anna Miles at Auckland Hospital

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